Comparison of the distribution of combined immunological and virological responses in adult HIV positive patients across Antiretroviral Therapy (ART) providers in Tshwane: a Multilevel Analysis

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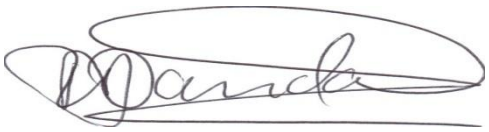
DECLARATION

I declare that the dissertation titled "Comparison of the distribution of combined immunological and virological responses in adult HIV positive patients across Antiretroviral Therapy (ART) providers in Tshwane: a Multilevel Analysis" that I am submitting for assessment is my own work and I have not before submitted it to any other institution of higher learning for any degree. It contains no section copied in whole or in part from any other source unless explicitly identified in quotation marks and with detailed, complete and accurate referencing.

The ethical approval for this study was granted on 2nd December 2010 and the reference number is S205/2010



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ACRONYMS AND ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
CD4	Cluster of Differentiation 4
DOH	Department of Health
FPD	Foundation for Professional development
GEE	Generalized Estimating Equations
HAART	Highly Active Antiretroviral therapy
HAST	HIV and AIDS / STI
HBV	Hepatitis B Virus
HGT	Blood Glucose Test
HIV	Human Immunodeficiency Virus
HTLV	The Human T-lymphotropic virus
LR	Logistic regression
LRD	Logistic regression with dummy variables for clinics
LRT	Likelihood ratio test
MLLR	Multilevel Logistic regression
OR	Odds ratio
PEPFAR	President's Emergency Plan for AIDS Relief
RE	Random effects
ROC	Receiver Operating Characteristics
SHSPH	School of Health Systems and Public Health
VL	Viral Load
WHO	World Health Organization

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ABSTRACT

Background: Immunological and virological responses to ART are important outcome indicators that are mostly used to evaluate the success of an ART program. A comparative performance between ART providers based on the two outcomes can be useful in optimising resources to underperforming providers and advising quality improvement plans.

Aim: To compare immunological and virological responses of ART for adult HIV positive patients between providers in Tshwane District, Gauteng Province, South Africa.

Methodology: This study was an analytical observational study that retrospectively compared patient treatment outcomes on immunological and virological responses between 16 Antiretroviral Therapy (ART) providers. The analysis compared baseline patients' status on these two outcomes with their statuses after 6 and12 months on ART. Ordinary logistic regression was used to calculate Standardised Incidence Ratios (SIR), while multilevel model analysis was used to calculate specific provider random effects of poor immunological and virological responses.

Results: After 6 months of treatment, the SIR of poor immunological outcome for all clinics under study, as predicted by the unadjusted logistic regression models was 0.29 (95% CI: 0.27-0.31), but varied from a low of 0.14 (95% CI: 0.00-0.40) to a high of 0.66 (95% CI: 0.13-1.20) between the clinics. Two clinics had a Standardised Incidence Ratio (SIR) of poor immunological response that was significantly below 1 (poor immunological rate below average), while three clinics had an SIR above 1 (poor immunological rate above average) under the unadjusted logistic models. After adjusting for the effects of gender, age, drug combination, religion and present virological status, no clinic had a SIR that was significantly below 1, but two clinics had a SIR that was significantly above 1.

Under the logistic multilevel (MLLR) analysis, the unadjusted model flagged two clinics whose clinic specific effects were below zero (lower rate of poor immunological outcome below that of the total sample) and one clinic whose clinic specific effect was above zero (higher rate of poor immunological outcome below the total sample rate). The adjusted model showed that no clinic had residual effects that were significantly below or above zero. The confidence intervals for MLLR model were found not to be wider than those of the logistic regression (LR) models particularly for clinics with small sample sizes. A number of clinics changed the relative order of their SIR/random effects after case-mix adjustments under both the LR and MLLR modelling.

For poor virological response, both the LRD and MLLR models indicated no clinic specific effects. The predicted poor virological response rate by the case-mix unadjusted LR model was 0.12 (95% CI 0.11 - 0.13). All clinics except one had SIRs that were not significantly different from 1. After adjusting for CD4 count and age, no clinic had an SIR that was significantly different from 1.

Conclusions: Case-mix or patients baseline characteristics explained much of the variation in the Standardised Incidence Ratios (SIR) of poor immunological outcome after 6 months of patient treatment, while provider (clinic) specific effects explained much of the variation after 12 months of treatment. After 6 months of treatment, the results also showed that there were significant differences in the SIR between the clinics before case-mix adjustments, but the differences disappeared after case-mix adjustments. This shows that comparison of treatment outcomes between providers (clinics) can be misleading if no proper adjustment are made for confounding factors.

Differences in the SIRs for poor virological outcome, after 6 months of patient treatment were no longer significant between clinics after taking account of CD4 count and age.

Key terms: Immunological response, virological response, case-mix adjustment, SIR, clinic specific effects, LR, LRD and MLLR.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

The use of highly active antiretroviral therapy (HAART) has proved to slow progression of the human immunodeficiency virus (HIV) infection towards acquired immunodeficiency syndrome (AIDS) leading to marked reduction in morbidities, mortalities, opportunistic infections and HIV transmission in infected patients[1,2]. Antiretroviral therapy also enables HIV patients to lead economically productive lives[3] and to increase in life expectancy[4]. These desirable outcomes are achieved through immunological recovery indicated with an increase in CD4 T-cell count and viral suppression to undetectable levels. CD4 T-cell counts and viral load are the most commonly used indicators for monitoring the effectiveness of antiretroviral treatment, disease prognosis and are also the main predictors of treatment failure in HIV infected patients[5-8].

In 2011, an estimated 56% of people eligible (CD4 cell count ≤ 500 cells/mm³) for HIV treatment in sub-Saharan Africa were on treatment with Benin, Kenya, Malawi, South Africa and Zimbabwe achieving more than 60% coverage[9]. South Africa alone has one of the largest antiretroviral therapy (ART) programmes worldwide, with the estimated number of patients receiving ART rising to 1.79 million by mid 2011[10]. Given the tremendous scale-up of this initiative there is continuous need to evaluate the outcomes of ART programme in order to improve quality of services. In an endeavour to achieve this, studies have been done that evaluate ART outcome differences by for example age[11,12] and gender[13,14] among other factors.

An area that has received little attention is assessment of differences in treatment outcomes such as immunological and virological responses across ART providers. A number of studies[12,13,15-19] investigating variation of ART outcomes of survival/death, virological and immunological response rates by various factors such as gender and age, have been done by pooling data from different

sites/programs, but without accounting for differences in the outcome of interest between the sites/programs, consequently ignoring clustering of treatment subjects and thus assuming no site/program effects. The pooled number of sites/programs in some of these studies has ranged from a low of 2[18] to a high of 55[19]. However, in one study[20], multilevel analysis[21,22] was used to investigate the effect of several program-level (e.g. urban/rural setting, type of facility, HIV services provided, etc) and contextual-level (e.g. proportions of people with AIDS knowledge, transmission and protection) factors on aggregated patient data (median CD4+ cell count) at the program-level using data from several treatment sites and cohorts.

There may be reasons to believe that ART providers may vary in the proportion of patients who respond immunologically or virologically. This is because providers usually differ in many aspects such as human and infrastructural resource capacity, adherence to protocol and provider-patient interactions among other provider specific factors. In most ART settings since such provider specific factors are rarely known or measured, they are not accounted for in many studies when analysing factors that affect treatment outcomes. To account for the unknown and unmeasured factors relating to providers, the analysis in this study included a provider specific random effect (assumed to vary by providers) in addition to other known risk factors, and investigated its effect on the treatment outcomes under study. Multilevel or random effects logistic regression model was used for the analysis and compared with ordinary linear logistic regression. The outcomes for CD4 count and viral load were categorised as either poor or good as discussed in section 3.3.

1.1.1 Antiretroviral (ARV) program data and multilevel analysis

The ART outcome indicators may vary across providers/clinics due to the composition of patients within them or due to differences between providers in terms of resources and cultures within the various ART clinics. This implies that some of the variation in any of these indicators is at the patient level and some at the provider level. Patient characteristics may explain some variation at both the

individual and provider levels. For example, the literature has shown that poor immunological response rate is more prevalent among older and male patients[11,14,23,24]. Providers serving such patients, despite having good clinical management teams, could therefore show low success rates compared to providers serving younger female patients.

Adjusting for patient characteristics (case-mix adjustment) may reduce the variation in poor rates of patient outcomes between providers. Case-mix refers to the factors that characterise the patient population such as age, sex, severity of disease or initial diagnosis[25]. Case-mix adjustments are made to account for the differences in provider performances attributable solely to differences in the populations served with the hope that the remaining differences in outcome between providers reflect the quality of care[25,26]. While case-mix adjustment is quite possible and commonly done in the ordinary logistic regression analysis, proponents of multilevel data analysis have given some advantages associated with the latter methodology when comparing institutional performances[25-27] which include:

i) adjusting for risks associated with each level unlike the standard profiling methods which ignore the hierarchical nature of data
ii) it allows the probability of acceptable provider performance to be calculated
iii) providers with small sample sizes remain in the analysis since their estimated values are pulled towards the average

Multilevel modelling has been used in rating health care providers for a number of performance indicators including mortality rates of certain diseases[28-30], patient satisfaction with health care[31,32], and immunisation uptake[33].

In the present study, patients' immunological and virological treatment outcomes, labelled as either "Good" or "Poor" as described in section 3.3 are modelled using logistic regression based on the patients' case-mix. In the multilevel analysis, a specific provider effect is added to this model to capture all the provider's unmeasured/unobserved covariates. The aim is to quantify the excess risk of poor outcome (provider specific effect above 0 or below 0). The provider specific

effect is assumed normally distributed with a zero mean and unknown variance on the logit scale. An effect with a value above zero indicates a worse outcome than the average, while a provider specific effect value below zero will indicate a better outcome than the average value of zero. The health public policy issue will then try to explain how the providers find themselves with wide variations in risk if random effects are shown to vary widely.

Based on the preceding discussion, the aim of this study was to compare immunological and virological response rates between ART providers in Tshwane District after accounting for known baseline patient factors.

1.1.2 Health care quality improvement

Quality measures can be used for several general purposes, chief amongst them being quality improvement, accountability and research within and without an organization[34]. When measured for quality improvement purposes, it can be used for both within an institution or system of care (internal quality improvement) or across institutions or systems of care (external quality improvement). An internal quality improvement procedure for say immunological response would generally involve getting the percentage of patients whose CD4+ T cells have increased by a given predetermined value from the baseline. This comparison can be done over time, for example at 6, 12 or 24 months for cohorts of patients within the same provider. This kind of internal benchmark would provide motivation for change and also enable prioritization of areas for quality improvement.

However, relying solely on internal benchmarking may not necessary capture best practices outside the provider[35]. Quality measures based on external benchmarks use comparative data between providers to gauge performance that can be useful in identifying improvements that have proven to be successful in other providers. The major users of results of external quality improvement are therefore the participating providers of care within a given program (regional or national). External agencies such as the Foundation for Programme Development (FPD) that have repositories of regularly collected patient outcome data can, after verifying its accuracy, use it to report quality performance results

among providers of care in a format that allows for their direct comparison. External agencies may also make comparative data results available that can then be used to encourage performance at the best achievable level.

The findings in this study can be used for both internal and external quality improvement in the delivery of HIV/AIDS treatment and care for the ART providers under comparison.

1.2 LITERATURE REVIEW

1.2.1 Goals of antiretroviral therapy (ART)

The primary goals for initiating antiretroviral therapy (ART) are to 1) reduce HIV-associated morbidity and mortalities, 2) provide an opportunity for people to be productive in their work and daily life, 3) restore and preserve immunologic function, 4) maximally and durably suppress plasma HIV viral load, and 5) prevent HIV transmission[36,37].

1.2.2 Measures of quality of care

The quality of health care provided to patients, how it is provided and with what it is provided is an agenda in most healthcare systems. To assess quality of healthcare, measures or indicators of quality will have to be defined and developed. An indicator in health care setup can be defined as a measure of program performance that is tracked over time by a monitoring system[38]. They are variables that measure the different aspects of a given program be it, inputs, processes, outputs, outcomes or impacts[39]. Donabedian[40] proposed three types of indicators (structural, process or outcome) for evaluating quality of medical care. Indicators related to structure include material resources (facilities, equipments, finances, bed capacity of a hospital etc), human resources such as number of nurses with training on how to manage HIV/AIDS patient, accessibility and availability of health care. Process indicators relate to what is actually done in giving and receiving care, i.e. the practitioner's activities in making a diagnosis, recommending or implementing treatment, or other interaction with the patient[41]. Outcomes are states of health or events that follow an encounter with healthcare

and that may be affected by it. Outcome measures may be important in quality improvement programs as they are more likely to point out the areas in which intervention could improve care[34]. An ideal outcome indicator is therefore expected to capture the effect of care processes on the health and wellbeing of patients and populations. Some characteristics of good indicators include validity, reliability and comparability across programs[39]; relevance and applicability, based on evidence, and flexibility of obtaining the indicator data[41].

It has been noted that in reality there are few measures of quality[42], although 'process measures are more sensitive to differences in the quality of care and are direct measures of quality'[43]. On the other hand 'outcome measures are of great intrinsic interest and can reflect all aspects of care, including those that are otherwise difficult to measure such as technical expertise and operator skills'[43]. In many health delivery situations, there are innumerable factors that could be associated with a patient's health outcome. In such situations, in order to improve the usefulness of outcome indicators, it is advisable that outcome measures are adjusted for factors like psychosocial characteristics, lifestyle factors and severity of the illness, if fair comparisons of the outcome are to be made. Risk adjustment is useful to control confounding factors that might contribute to the outcome indicator[44].

Based on this, it can be argued that patient treatment outcomes that meet quality requirements (validity, reliability, relevance and applicability, based on evidence, and the flexibility of obtaining the indicator data) can be used as indicators for comparing quality of care across healthcare providers.

1.2.3 Indicators relating to ART program success

The World Health Organisation (WHO) has defined a number of antiretroviral therapy (ART) success indicators[5]. These indicators which relate to patient's retention in the program, loss-to-follow-up, treatment regimens, functional status, CD4 count, viral load and weight gain are summarised (biannually for the first year of treatment, and then annually thereafter) in an ART cohort analysis report. Similar quality-of-care indicators, which include survival, immunological

measures, disease progression, symptoms, subjective health status, disability and health utility have also be documented elsewhere[45]. In a recent review article[44], 50 process-related indicators and 15 outcome related indicators were proposed for HIV/AIDS clinical care. Two of the outcome related indicators are CD4 count and maximal viral control.

1.2.4 Cluster of differentiation 4 (CD4) count and viral load (VL)

The median CD4 count for a group of patients is a good measure of immuno-suppression and a predictor of mortality and serious opportunistic infections (OIs)[5]. CD4 count is also helpful in monitoring patients' response to ART, evaluating possible treatment failure and making decisions on changing ART[5,46]. Different cut-off points for what can be considered successful immunological and virological responses have been used in various studies/literature. The cohort analysis form provided in the Patient Monitoring and Guidelines for HIV Care and ART[5] supports analyses of the percentage of patients with CD4 count of at least 200 cells/ml and viral loads of <400 copies/ml at each measurement time. Elsewhere, a successful immunologic response was indicated if there was an increase of at least 50 CD4 cells/ml[47,48]. In another study[49], patients with an increase from the pre-HAART CD4+ cell count of at least 100 cells/ml 6 to 12 months after the initiation of HAART were identified as immunological responders. Other cut-off points for poor immunological response are CD4 counts less than or equal to 350 cells/uL[50]; CD4 decline to or below baseline value, CD4 drop to less than 50% of peak on-treatment value or failure to achieve CD4 greater than 100 cells/ml[24] and CD4 counts ≤ 200 cells/uL[51,52]. Successful viral load response has been defined differently by different authors; less than 400 copies/ml[5,49,53-55], less than 500 copies/ml[47] and less than 1000 copies/ml[56].

Risk factors associated with poor immunological or virological responses have been discussed by various authors. Older age[11,13,14], infection by HIV–2 and drug toxicity, the use of the combination tenofovir/didanosine, use of zidovudine or didanosine as part of the antiretroviral regimen, the concurrent use of other

myelotoxic drugs such as co-trimoxazole or the presence of certain co-infections, such as HTLV-1 has been implicated in failure to increase CD4+ cell count despite viral suppression[57]. Poor adherence has been associated with poor virological response[17,56,58]. Other factors associated with poor virological outcomes are tuberculosis diagnosed after ART initiation and lower weight than at baseline[58] and younger age[23,48].

Immunological and virological outcomes have been studied both descriptively and analytically[53,56]. The analytical methods have mostly relied on linear or logistic regression to identify predictors of CD4 counts and viral loads[53,56]. Messou et al[17] analysed repeated measures data on CD4 count and viral load outcomes at each time point separately and so did not account for the clustering of the outcomes. Wouters et al[59] found a strong association between community factors (treatment buddy, i.e. relative or close friend of the patient, community health worker (CHW), and HIV/AIDS support group, e.g. church membership) and patient's immunologic and virologic responses while on ART at each occasion (6, 12 and 24 months). Effect of hepatitis B virus (HBV) on viral load suppression, change in CD4 cell count, mortality, and hepatotoxicity was assessed using logistic regression for univariate analysis as well as generalized estimating equations (GEE) for repeated measures[60]. In this study, the investigators found no association between HBV status and HIV RNA suppression, CD4 cell count response, or mortality during the first 72 weeks of HAART in an African setting. Linear mixed effect (multilevel analysis) models, like the GEE also account for clustering of observations from the same patient. These methods have been used in a number of studies to examine the relationship between CD4 counts and viral load outcomes with various covariates (demographic and baseline characteristics)[61-65]. In Melekhin et al[61], better results for both viral load and CD4 count outcomes were reported after 6-month of treatment in a cohort of pregnant women initiating high antiretroviral therapy (HAART) before pregnancy than for those initiating after pregnancy while Liu et al[62] reported a highly significant association between percentage of adherence and low viral load after 48 weeks (approximately 11 months) of ARV treatment.

CHAPTER TWO

RESEARCH PROBLEM

2.1 DEFINITION OF THE RESEARCH PROBLEM

Evaluation studies provide credible information for use in improving programs, identifying lessons learned, and informing decisions about future resource allocation. The main objective of health provider profiling is to estimate and compare provider-specific performance measures of utilization/cost, process, clinical outcomes and patient satisfaction/quality of life (QoL) using a normative (external) or a relative (internal) standard[29,66]. Standard health provider profiling compares crude performance measures without accounting for the differences existing in the populations served by healthcare providers. In ART, as with any other healthcare provision, patients are nested within providers, who in turn are nested within administrative regions. This implies that the outcome of each indicator can vary due to patients' characteristics as well as due to provider characteristics. When data is analysed at group level, it can suffer from an ecological fallacy[27,67-69]. This arises when confounding factors, operating either within or between groups under comparison are not accounted for in the analysis[67]. Differences in the outcome of interest may reflect differences in the composition of the patient population as well as differences in the clinical management teams.

The research problem in this study is that, it has been found that in many studies that use data from multiple groups (e.g. clinics), correlation of subjects within the groups is ignored and not accounted for in the analysis of factors that affect ART health outcomes. Secondly, although certain studies have reported that immunological and virological response rates in their findings are comparable to other program/studies, no attempts have been made to account for patient differences across the programs in order to make fair comparisons. This research therefore tries to answer the research question: "Is the distribution of immunological and virological response rate homogeneous across providers in

the ART program under study, after accounting for the confounding patient characteristics?"

2.2 JUSTIFICATION OF THE STUDY

This research is primarily conducted as compulsory requirement for MSc degree in the school of Health Systems and Public Health (SHSPH), University of Pretoria. Nevertheless, in its own standing, the research has an important dimension in addressing a health problem and specifically in evaluation of public health programs. The importance of health program evaluation has briefly been discussed above. In this study, the primary aim is to compare the rates of poor treatment outcomes at the ART provider level. This we do using both ordinary logistic regression and hierarchical/ multilevel model analyses.

Multilevel modelling has traditionally been used in educational research where hierarchies exist naturally; students nested within classrooms, classrooms nested within schools and schools nested within administrative regions[70]. The last one and half decades has nevertheless witnessed a significant increase in the number of published articles that address public health problems using multilevel analysis[26-33,71-74]. Specifically, it has been noted that the methodology (multilevel analysis) is a new statistical approach that has not been widely employed in profiling of clinical centres' performances[28]. As noted from the literature review, much of practical application of multilevel analysis has been used to profile mortality rates and to a lesser extent patient satisfaction with healthcare provision and immunisation uptake. In addition, most of the work has been concentrated in the developed countries. Antiretroviral roll-out being a recent healthcare intervention provides a host of health outcomes that call for evaluation to find out to what extent program goals have been achieved. As noted earlier, these health outcomes can be explained by the various levels (patient, provider etc) that characterise the healthcare provision. It is therefore ideal to use an analytical method that takes into account the different sources of variation in order to make credible evaluation profiles. This is the main objective of this study.

2.3 RELEVANCE OF THE STUDY

One of the main focus areas of the Foundation for Professional Development (FPD) is to promote action research that would help health management make informed decisions. They specifically provide management support to health facility managers and Department of Health (DOH) officials in areas such as linking and expansion of HIV/AIDS services; integration of the health management information systems and improvement of monitoring and evaluation capacity. FPD supports expansion of the HIV/AIDS services through the Treatment, Care and Support Department formerly known as the Positive Life Project that provides ARV services to several clinics in South Africa.

This study focuses on one aspect of program evaluation, that is, outcome (summative) evaluation, and specifically assesses the extent to which the health status of the served population is influenced by the program activities (specifically ART). It is therefore anticipated that the findings of this study will highlight the performance of immunological and virological indicators between the providers relative to each other and consequently provide information that could be necessary for improving service delivery for the FPD ART program.

2.4 AIM OF THE STUDY

The aim of this study was to compare immunological and virological response rates between antiretroviral therapy (ART) providers supported by the Foundation for Programme Development (FPD) in Tshwane District at 6 and 12 months of treatment after adjusting for confounding factors.

2.4.1 Objectives of the Study

1. to examine the factors associated with immunological and virological responses that can be used as case-mix adjusters before comparing provider performances on these outcomes
2. to investigate the effect of provider profiles on immunological and virological outcomes using both logistic regression and multilevel analysis after adjusting for the case-mix

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN

This study was a retrospective cohort study reviewing patient treatment data from an ART database. The analysis compared the proportions of patients with either immunological or virological failure at 6 months and at 12 months between ART providers, before and after adjusting for baseline patient-level characteristics. Antiretroviral Therapy (ART) data can be viewed as arising from a single arm clinical trial or a quasi-experimental study design. Quasi-experimental study designs are common to many programme evaluation activities that involve before-after outcome measurements[67].

3.2 STUDY POPULATION AND SAMPLE SIZE

The study population consisted of a cohort of patients above 12 years old, who initiated therapy between October 2008 and January 2009 irrespective of baseline CD4 count or WHO disease stage. The start of the period is chosen to agree with the calendar of the President's Emergency Plan for AIDS Relief (PEPFAR) that supports FPD projects. All clinics supported by the FPD at the time of data acquisition were included in the study. As of February 2010, the Positive Life Project (FPD Treatment, Care and Support Department) was actively supporting a total of 19 service outlets providing ART. Three of the 19 clinics were excluded since one of them had no patients with CD4/VL measurements, and the other two had only one patient with either of the measurements.

The total sample size of the patient records for the 16 clinics used in the study was 3613. The sample sizes for the 16 clinics varied greatly with 4 clinics having less than 30 patients, 3 clinics had patients between 40 and 60, 4 had between 100 and 200 patients, and the remaining 5 clinics had more than 500 patients. The clinics with small sample size are retained in the study in order to make comparisons of estimates from both logistic regression and multilevel models.

The Foundation for Professional Development (FPD) facilitated acquisition of the data needed for this research.

3.3 PRIMARY STUDY VARIABLE

The primary study variables are immunological and virological responses to ART. After commencement of treatment, these two outcomes are monitored after approximately 6 months for the first year and then annually thereafter. In this study, patients' immunological and virological outcome rates disaggregated at the provider level were studied for the first two time points, that is, after 6 (4-9 month window) and 12 months (10-15 month window) of treatment. The World Health Organization (WHO) ART guidelines[75] are used to define a poor immunological response as (1) CD4 count below 100 cells/mm^3 after 6 or more months of therapy, or (2) a return to, or a fall below, the pre-therapy CD4 count after at least 6 months of therapy, or (3) a 50% decline from the on-treatment peak CD4 value. A poor virological response was determined if the level of plasma HIV viral RNA (viral load) is detectable (> 400 copies/ml)[5,49,53] after 6 or more months of treatment.

3.4 CASE-MIX ADJUSTERS

The outcomes of interest in this study were immunological and virological responses after approximately 6 and 12 months of ARV treatment. Case-mix adjustment was considered as confounder since it may be associated with the outcomes and is outside the influence of the actions within the ART providers. The factors used as confounders and that were jointly available to all patients and clinics are: age, sex, marital status, adherence to treatment, drug combination, baseline viral load and religion. Co-morbidities and other opportunistic infections could not be accounted for in the analysis since they were not uniformly captured into the database by all the clinics. These co-morbidities include; TB status, anaemia, cardiovascular (CVS) disease, cyanosis, Ear, Nose and Throat (ENT) infections, Jaundice, respiratory diseases, uro-genital and blood glucose test (HGT)

3.5 STATISTICAL DATA ANALYSIS

Univariate analysis was used to compute crude odds ratios for all potential confounding factors to be included in the single-level multiple logistic regression analysis. Two versions of the ordinary logistic regression model, without (referred in this study as LR) and with dummy variables (referred in this study as LRD) for clinics were employed, before and after case-mix adjustments to compare the disaggregated poor immunological and virological response rates between the ART providers.

The accuracy of the two multiple regression models (LR &LRD) was assessed using the Hosmer-Lemeshow goodness-of-fit test[76]. To evaluate the models' discriminative ability to predict immunological and virological responses, the area under the Receiver Operating Curve (ROC) was measured.

The best identified logistic regression (LR) model was used to obtain each patient's predicted probability of poor immunological and poor virological response. Expected number of a poor outcome for each provider was obtained by summing the predicted probability of the poor outcomes for all patients served by that provider[77]. This expected number of poor immunological or virological responders was compared with the observed number of the same outcome by taking the observed to expected ratio and terming it the Standardised Incidence Ratio (SIR). Providers that had a SIR that is significantly higher or lower than 1 were identified as either high (higher poor outcome rate than the average rate of all providers) or low (lower poor outcome rate than average) outliers. Standard errors of the SIRs were also computed in order to obtain confidence intervals for identifying providers that are significantly different from 1. SIRs were then ordered ascending order by clinics.

The logistic regression model with dummy variables for clinics herein referred as LRD, just like the LR model fitted an adjusted logistic model, but in addition to the LR approach, it included an indicator for each clinic. Predicted probabilities of the outcome (poor immunological or poor virological rate) for each patient in the entire sample were then calculated as if they had been treated in each of the 16 clinics. The predicted probabilities for all patients were averaged for each clinic

across the overall sample to obtain marginal predicted probabilities (rates) for each clinic. The SIR for this method compared the predicted marginal rate to the overall sample rate, treating the clinic-specific marginal rates as random and the overall rate as fixed (because it is based on relatively large numbers). Standard errors of the obtained SIR were calculated in order to obtain confidence intervals for identifying clinics that are significantly different from 1.

After identifying the best set of patient-level confounders from the standard logistic model, a random effect for the variable that define the higher-level (i.e. clinics) was introduced to test the suitability of the hierarchical/multilevel logistic regression model[25], herein referred as the MLLR model. The MLLR regression model was used to examine the effect of patient-level variables and a specific clinic-level effect on the patient-level outcome (immunological and virological response) simultaneously.

The likelihood-ratio test was used to compare the single-level model (LR) with the two-level model (ML) while the Intra-class Correlation Coefficient (ICC) was used to estimate the proportion of variability in the outcome that is explained by the presence of providers in the observed population[71]. The provider-level residual (provider specific effects) obtained from the difference between the estimated provider-specific probability and the overall estimated probability of the outcome was used to compare individual provider performances. These provider specific effects were ordered from the smallest to the largest and graphically presented with their 95% confidence intervals.

The following model representation describes both the single-level and the two-level model, the only difference being in the assumptions of the provider effects γ_i . The model representation is used for the three models LR, LR-D and ML

$$\log it\,\{P(y_{ij}=1\,|\,X_{ij})\} = \beta X_{ij} + \gamma_i, \quad i=1,\ldots,M,\ j=1,\ldots,n_j$$

y_{ij} binary outcome of immunological or virological response for patient j in provider i

X_{ij} covariate (case-mix adjuster) describing the patients characteristics of patient j in provider i

β the regression coefficient describing the effect of the covariates and the intercept

γ_i the effect of provider i of which three assumptions can be made:

i. common provider effect $\gamma_1 = \gamma_2 = \ldots = \gamma_M$

ii. fixed effect assumption with respect to some overall mean, where a separate intercept is included for each provider

iii. the random effect assumption that the γ_i are drawn from a common distribution, e.g. normal distribution

The predicted probability of a poor outcome for each patient is given as

$$P(y_{ij} = 1 \mid X_{ij}) = \frac{\exp(\beta X_{ij})}{1 + \exp(\beta X_{ij})}$$

All analyses in this study were done using Stata 12 SE edition[78] using the appropriate statistical methods.

3.6 ETHICS

The study was approved by the Research Ethics Committee; Faculty of Health Sciences, University of the Pretoria on 02/12/2010. Permission to use the data was granted by the Tshwane District Health Department, while the actual data was provided by its custodian, the Foundation for Programme Development (FPD).

The investigator was required to sign an agreement with FPD to respect patient's privacy and confidentiality and to abide by rules and regulations relating to data security. The FPD database administrator insured that all records provided did not include patient's names, addresses or any other contact details

CHAPTER FOUR

RESULTS

There were 2678 patient records after treatment for approximately 6 months (4-9 months window) from a total of 15 clinics. The number of patient records was 935 after 12 (9-15) months of treatment. Definition of a poor immunological response was based on the change in CD4 count between baseline measurement and a subsequent on treatment measurement at 6 and 12 months or difference between two subsequent on treatment times as described in section 3.3.

4.1 DISTRIBUTION OF CASE-MIX ADJUSTERS

Table 1: Case-mix and outcomes after 6 and 12 months of treatment

Factor		Treatment period			
		6 Month		12 Month	
		Number	***%***	***Number***	***%***
Patient's gender	Female	1815	68%	638	68%
	Male	863	32%	297	32%
Religion	Other	886	33%	309	33%
	Christian	1792	67%	626	67%
Marital status	Single	1901	71%	661	71%
	Married	631	24%	213	23%
	Divorced/Widowed	146	5%	61	7%
Regimen	d4T based	2283	85%	760	81%
	AZT/ZDV based	157	6%	86	9%
	TDF based	238	9%	89	10%
Age category	13-30	630	24%	215	23%
	31-45	1549	58%	543	58%
	46-72	499	19%	177	19%
Immunological outcome	Good	1901	71%	785	84%
	Poor	777	29%	150	16%
Virological outcome	Good	2368	88%	812	87%
	Poor	310	12%	123	13%
Total		**2678**	**100%**	**935**	**100%**

As shown on Table 1, the distribution of the patient characteristics/risk factors remained almost the same between the two treatment periods. However, there is a notable difference in the distribution of immunological outcome between the

two treatment periods, whereby the rate of poor response is higher (29%) after 6 months than after 12 months of treatment (16%).

4.1.1 Case-mix distribution by clinics

Table 2 and Table 3 report the distribution of patient characteristics by clinic. After 6 months of treatment (Table 2), four clinics (CUL, DKC, LRH and FOH) had percentages of male patients that were higher than the overall percentage for all clinics combined. CUL and FOH again, together with LRH had the highest percentages (≥ 80%) of patients whose age was at least 30 years at baseline. In terms of drug regimen, FOH, LRH and DGM had the highest percentages (higher than the overall percentage of 2%) of patients who were on AZT/ZDV based regimen. The lowest percentage of Christian patients was found at JUB (10%) and highest in KTM and CUL at 95% and 96% respectively.

After 12 months of treatment (Table 3), percentage of male patients was again highest in CUL and lowest in LAU, while those whose baseline age was more than 30 years were more prevalent in STB (84%) and PDS (87%). DGM and FOH had more patients on AZT/ZDV based regimen compared with the other clinics. Christian patients were again lowest at JUB (8%) and highest at CUL (94%) and STB (97%).

Table 2: Summaries of case-mix by clinics after 6 months of treatment

Factor	CUL 158	DGM 35	DKC 90	FOH 25	JUB 311	KAL 3	KGH 2	KTM 375	LAU 602	LRH 42	ODI 441	PAH 450	PDS 7	PWH 10	STB 127	Total 2678
Gender	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	**No.**
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	**%**
Female	98	30	55	13	212	1	2	256	430	23	285	307	5	7	91	**1815**
	62%	86%	61%	52%	68%	33%	100%	68%	71%	55%	65%	68%	71%	70%	72%	**68%**
Male	60	5	35	12	99	2	0	119	172	19	156	143	2	3	36	**863**
	38%	14%	39%	48%	32%	67%	0%	32%	29%	45%	35%	32%	29%	30%	28%	**32%**
Age category																
13-30	31	14	25	3	71	0	1	87	128	5	109	119	1	2	34	**630**
	20%	40%	28%	12%	23%	0%	50%	23%	21%	12%	25%	26%	14%	20%	27%	**24%**
31-45	90	20	40	19	169	2	1	228	364	30	254	252	6	6	68	**1549**
	57%	57%	44%	76%	54%	67%	50%	61%	61%	71%	58%	56%	86%	60%	54%	**58%**
46-72	37	1	25	3	71	1	0	60	110	7	78	79	0	2	25	**499**
	23%	3%	28%	12%	23%	33%	0%	16%	18%	17%	18%	18%	0%	20%	20%	**19%**
Drug combination																
d4T based	120	28	69	2	278	3	1	288	541	22	414	393	4	6	114	**2283**
	76%	80%	77%	8%	89%	100%	50%	77%	90%	52%	94%	87%	57%	60%	90%	**85%**
AZT/ZDV based	28	7	8	6	10	0	1	16	21	4	10	33	3	0	10	**157**
	18%	20%	9%	24%	4%	0%	50%	4%	3%	10%	3%	7%	43%	0%	8%	**6%**
TDF based	10	0	13	17	23	0	0	71	40	16	17	24	0	4	3	**238**
	6%	0%	14%	68%	7%	0%	0%	19%	7%	38%	4%	5%	0%	40%	2%	**9%**
Religion																
Other	6	13	2	8	279	1	1	17	128	7	141	264	0	8	11	**886**
	4%	37%	2%	32%	90%	33%	50%	5%	21%	17%	32%	59%	0%	80%	9%	**33%**
Christian	152	22	88	17	32	2	1	358	474	35	300	186	7	2	116	**1792**
	96%	63%	98%	68%	10%	67%	50%	95%	79%	83%	68%	41%	100%	20%	91%	**67%**
Virological response																
Good	137	28	81	24	270	2	2	335	531	33	392	408	6	9	110	**2368**
	87%	80%	90%	96%	87%	67%	100%	89%	88%	79%	89%	91%	86%	90%	87%	**88%**
Poor	21	7	9	1	41	1	0	40	71	9	49	42	1	1	17	**310**
	13%	20%	10%	4%	13%	33%	0%	11%	12%	21%	11%	9%	14%	10%	13%	**12%**

Table 3: Summaries of case-mix by clinics after 12 months of treatment

Factor	CUL 51	DGM 53	DKC 44	FOH 16	JUB 145	KGH 5	KTM 180	LAU 139	LRH 14	MAM 2	ODI 167	PAH 53	PDS 30	PWH 4	STB 32	Total 935
Gender	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	**No. %**
Female	25 49%	36 68%	29 66%	10 63%	100 69%	5 100%	129 72%	102 73%	7 50%	2 100%	110 66%	38 72%	21 70%	3 75%	21 66%	**638 68%**
Male	26 51%	17 32%	15 34%	6 38%	45 31%	0 0%	51 28%	37 27%	7 50%	0 0%	57 34%	15 28%	9 30%	1 25%	11 34%	**297 32%**
Age category																
13-30	10 20%	10 19%	12 27%	3 19%	35 24%	0 0%	49 27%	37 27%	1 7%	1 50%	33 20%	13 25%	4 13%	2 50%	5 16%	**215 23%**
31-45	25 49%	27 51%	26 59%	11 69%	86 59%	4 80%	100 56%	80 58%	11 79%	1 50%	103 62%	34 64%	17 57%	2 50%	16 50%	**543 58%**
46-72	16 31%	16 30%	6 14%	2 13%	24 17%	1 20%	31 17%	22 16%	2 14%	0 0%	31 19%	6 11%	9 30%	0 0%	11 34%	**177 19%**
Drug combination																
d4T based	40 78%	33 62%	36 82%	1 6%	117 81%	4 80%	152 84%	128 92%	7 50%	0 0%	141 84%	40 76%	27 90%	4 100%	30 94%	**760 81%**
AZT/ZDV based	5 10%	16 30%	8 18%	4 25%	6 4%	1 20%	17 9%	6 4%	1 7%	0 0%	11 7%	8 15%	3 10%	0 0%	0 0%	**86 9%**
TDF based	6 12%	4 8%	0 0%	11 69%	22 15%	0 0%	11 6%	5 4%	6 43%	2 100%	15 9%	5 9%	0 0%	0 0%	2 6%	**89 10%**
Religion																
Other	3 6%	35 66%	0 0%	3 19%	133 92%	1 20%	10 6%	29 21%	1 7%	0 0%	56 34%	33 62%	0 0%	4 100%	1 3%	**309 33%**
Christian	48 94%	18 34%	44 100%	13 81%	12 8%	4 80%	170 94%	110 79%	13 93%	2 100%	111 67%	20 38%	30 100%	0 0%	31 97%	**626 67%**
Virological response																
Good	46 90%	42 79%	37 84%	16 100%	127 88%	5 100%	157 87%	122 88%	13 93%	2 100%	139 83%	44 83%	28 93%	4 100%	30 94%	**812 87%**
Poor	5 10%	11 21%	7 16%	0 0%	18 12%	0 0%	23 13%	17 12%	1 7%	0 0%	28 17%	9 17%	2 7%	0 0%	2 6%	**123 13%**

4.2 IMMUNOLOGICAL RESPONSE

The study first describes CD4 count at baseline, 6 months and 12 months in relation to some risk factors such as age and gender that are known to affect its outcome, and are also available at the two patient observation times.

Table 4: Median CD4 count by patient characteristics at baseline

Factor	Baseline	6 month	12 month	Total (on treatment)
Gender				
Female	142	251	298	262
Male	128	210	236	217
Religion				
Other	123	248	286	257
Christian	143	236	276	245
Age category (Years)				
13-30	152	267	316	279
31-45	135	236	273	248
46-72	130	220	247	227
Marital status				
Single	138	241	273	250
Married	134	238	286	249
Divorced/Widowed	144	242	284	255
Total	**137**	**240**	**277**	**250**

On average males initiated treatment at a lower median CD4 count compared to females, and consequently maintained a low count for measurements made after 6 and 12 months of treatment. Similarly younger patients' CD4 counts were higher than for respective older patients at the two observation periods. Patients whose religion is Christianity on average started therapy at a slightly higher CD4 count compared with patients in other religions, but their median on treatment CD4 count was lower than that of their counterparts.

4.2.1 Univariate Analysis

Four of the five factors available for case-mix adjustment namely gender, religion, drug regimen and virological status were identified by the univariate model analysis as being associated with immunological outcome at both 6 and 12

months of treatment (Table 5). Marital status is the only case-mix adjuster that did not have an association with poor immunological response after both 6 and 12 months of treatment.

Table 5: OR of poor immunological outcome by case-mix: univariate analysis

Factor	6 months			12 months		
	Odds Ratio	Pr	95% CI	Odds Ratio	Pr	95% CI
Gender						
Male	1.64	0.000	1.38 - 1.96	2.3	0.000	1.61 - 3.28
Religion						
Christian vs. Other	1.64	0.000	1.36 - 1.98	1.49	0.000	1.27 - 1.76
Marital status (vs. Single)						
Married	0.94	0.532	0.77 - 1.15	0.78	0.272	0.50 - 1.21
Divorced/Widowed	0.97	0.881	0.67 - 1.41	0.97	0.936	0.50 - 1.97
Regimen (vs. d4T based)						
AZT/ZDV based	1.88	0.000	1.38 - 2.62	2.07	0.006	1.23 – 3.47
TDF based	0.93	0.647	0.69 - 1.26	0.97	0.922	0.52 - 1.80
Age (vs. 13-30 yrs)						
31-45	1.36	0.005	1.10 - 1.68	1.24	0.378	0.77 - 1.98
46-72	1.58	0.001	1.22 - 2.05	2.48	0.001	1.46 - 4.22
Virological status (vs. Good)						
Poor	2.17	0.000	1.70 - 2.76	1.67	0.031	1.05 - 2.65

The odds ratio of poor immunological outcome for male gender, AZT based regimen and age (46-72 years) increased, while those of religion, the 31-41 years age group, and virological status decreased with time of treatment.

4.2.2 Immunological outcome by clinic

For all the clinics put together, the percentage of poor immunological response was 29% at 6 months and 16% at 12 months of treatment. Of the ten clinics with acceptable sample sizes (>30), only three clinics (JUB-20%, PAH-24% and LAU-28%) had crude (unadjusted) poor immunological rates that were below the overall rate (29%) after 6 months of treatment, while after 12 months of treatment, the clinics that had an unadjusted poor immunological response rates above the overall rate (16%) increased to five. Of the 10 clinics with acceptable sample sizes, JUB had the lowest crude percentage (20%), while DKC had the

highest percentage (43%) of poor immunological outcome after 6 months of treatment. Four clinics, namely KAL, KGH, MAM, and PWH each had combined (6 and 12 months) sample sizes that were much smaller compared with the other clinics. The rate of poor immunological outcome for all clinics except for PDS dropped substantially (below the average rate after 6 months of treatment) after 12 months of treatment compared with the same outcome after 6 months of treatment.

Table 6: Immunological response rates by clinics

Clinic	6 months			12 months		
	Good	Poor	Total	Good	Poor	Total
	No. (%)	*No. (%)*	***No. (%)***	*No. (%)*	*No. (%)*	***No. (%)***
CUL	109 (69%)	49 (31%)	**158 (100%)**	43 (84%)	8 (16%)	**51 (100%)**
DGM	23 (66%)	12 (34%)	**35 (100%)**	38 (72%)	15 (28%)	**53 (100%)**
DKC	51 (57%)	39 (43%)	**90 (100%)**	29 (66%)	15 (34%)	**44 (100%)**
FOH	16 (64%)	9 (36%)	**25 (100%)**	16 (100%)	0 (0%)	**16 (100%)**
JUB	250 (80%)	61 (20%)	**311 (100%)**	125 (86%)	20 (14%)	**145 (100%)**
KAL	1 (33%)	2 (67%)	**3 (100%)**	(0%)	(0%)	**(0%)**
KGH	1 (50%)	1 (50%)	**2 (100%)**	3 (60%)	2 (40%)	**5 (100%)**
KTM	242 (65%)	133 (35%)	**375 (100%)**	161 (89%)	19 (11%)	**180 (100%)**
LAU	436 (72%)	166 (28%)	**602 (100%)**	128 (92%)	11 (8%)	**139 (100%)**
LRH	25 (60%)	17 (40%)	**42 (100%)**	12 (86%)	2 (14%)	**14 (100%)**
MAM	(0%)	(0%)	**(0%)**	1 (50%)	1 (50%)	**2 (100%)**
ODI	313 (71%)	128 (29%)	**441 (100%)**	126 (75%)	41 (25%)	**167 (100%)**
PAH	342 (76%)	108 (24%)	**450 (100%)**	52 (98%)	1 (2%)	**53 (100%)**
PDS	6 (86%)	1 (14%)	**7 (100%)**	19 (63%)	11 (37%)	**30 (100%)**
PWH	7 (70%)	3 (30%)	**10 (100%)**	4 (100%)	0 (0%)	**4 (100%)**
STB	79 (62%)	48 (38%)	**127 (100%)**	28 (88%)	4 (13%)	**32 (100%)**
Total	**1901 (71%)**	**777 (29%)**	**2678 (100%)**	**785 (84%)**	**150 (16%)**	**935 (100%)**

After 6 months of treatment, JUB had the lowest unadjusted and adjusted standardised incidence ratio (SIR) amongst the 10 clinics with relatively large sample sizes. A shown on Table 7, with JUB as the baseline clinic, the adjusted odds ratios are lower than the unadjusted odds ratios for all the clinics except PWH.

Table 7: Unadjusted and adjusted OR of poor immunological response by clinic: 6 months

Clinic		Unadjusted odds ratios			Adjusted odds ratios		
	N	*OR*	*Prob.*	*95% CI*	*OR*	*Prob.*	*95% CI*
CUL	158	1.8	0.006	(1.2, 2.9)	1.3	0.372	(0.8, 2.0)
DGM	35	2.1	0.005	(1.0, 4.5)	1.8	0.139	(0.8, 4.0)
DKC	90	3.1	0.000	(1.9, 5.2)	2.3	0.003	(1.3, 4.1)
FOH	25	2.3	0.058	(0.97, 5.4)	1.7	0.283	(0.7, 4.3)
JUB	311	1.0					
KAL	3	8.1	0.088	(0.7, 98.9)	4.8	0.207	(0.4, 53.7)
KGH	2	4.1	0.321	(0.3, 66.5)	3.2	0.428	(0.2, 58.9)
KTM	375	2.3	0.000	(1.6, 3.2)	1.9	0.003	(1.2, 2.8)
LAU	602	1.5	0.009	(1.1, 2.2)	1.3	0.175	(0.9, 1.9)
LRH	42	2.8	0.003	(1.4, 5.5)	1.9	0.090	(0.9, 3.9)
MAM	-	-	-	-	-	-	-
ODI	441	1.7	0.004	(1.2, 2.4)	1.4	0.065	(1.0, 2.1)
PAH	450	1.3	0.153	(0.9, 1.8)	1.2	0.322	(0.8, 1.7)
PDS	7	0.7	0.726	(0.08, 5.8)	0.4	0.423	(0.0, 3.7)
PWH	10	1.8	0.424	(0.44, 7.0)	2.0	0.349	(0.5, 8.0)
STB	127	2.5	0.000	(1.6, 3.9)	2.0	0.008	(1.2, 3.2)

The likelihood ratio test between the two logistic models (LR and LRD), as well as that between LR and MLLR models, when unadjusted for case-mix, shows that there are significant differences in poor immunological response rates between the clinics.

Table 8: Case-mix unadjusted LRT statistic for clinic effects: 6 months

Model	Likelihood ratio statistic, prob.
LRD vs. LR	chi(14)=47.74, pr=0.0000
MLLR vs. LR	chibar(01)=19.24, pr=0.0000

4.2.3 Poor immunological rates (case-mix unadjusted): 6 months

The two types of models (LR&LRD) and MLLR are first used to compare poor immunological outcome rates by clinics before adjusting for case-mix.

4.2.3.1 Ordinary logistic regression (LR&LRD) models

Both the LR and LRD models without case-mix adjustment identified three clinics (KTM, STB and DKC) with more observed cases (SIR >1) of poor immunological responders than expected under the assumption of no differences in the response rates between the clinics. Two clinics (JUB and PAH) had SIRs that were below 1.

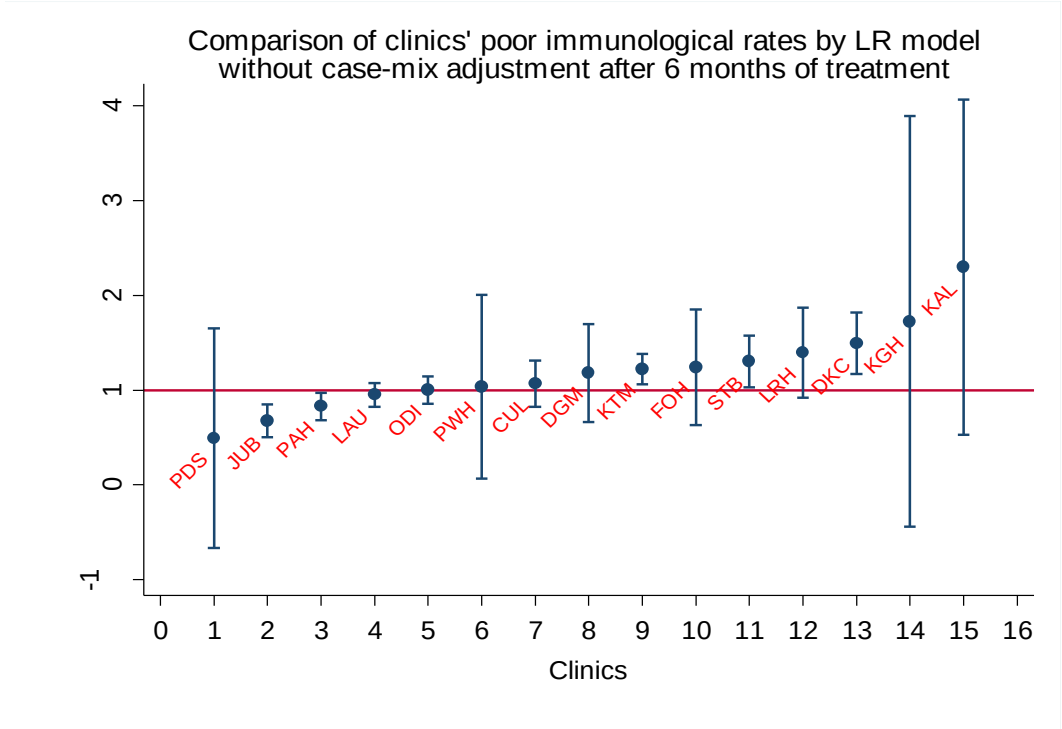

Figure 1: LR unadjusted SIRs of poor immunological outcome by clinics: 6 months

Seven clinics (about half the clinics) also had SIRs of poor immunological outcome that were significantly above that of JUB (clinic with the lowest SIR) before model adjustment. Similarly, the SIR of poor immunological response for PAH is significantly below that of KTM, STB and DKC. This is what is indicated by the likelihood ratio test statistic (chi(14)=47.74, pr=0.000) reported on Table 8.

4.2.3.2 Multilevel logistic regression (MLLR) model

The case-mix unadjusted multilevel logistic regression (MLLR) model, like the unadjusted LR/LRD models also identified two clinics (JUB and PAH) with poor immunological response rates (clinic's random effects below zero) that were below average. However, this model only flagged one clinic (DKC) as having clinic's random effects that were above zero after 6 months of treatment (Figure 2). The MLLR model identified three clinics (KTM, STB and DKC) that showed poor immunological response rates that were significantly above that of JUB (clinic with lowest poor immunological response rate after 6 months of treatment), unlike the LR/LRD models which identified seven clinics that had poor immunological rates that were significantly higher than that of JUB.

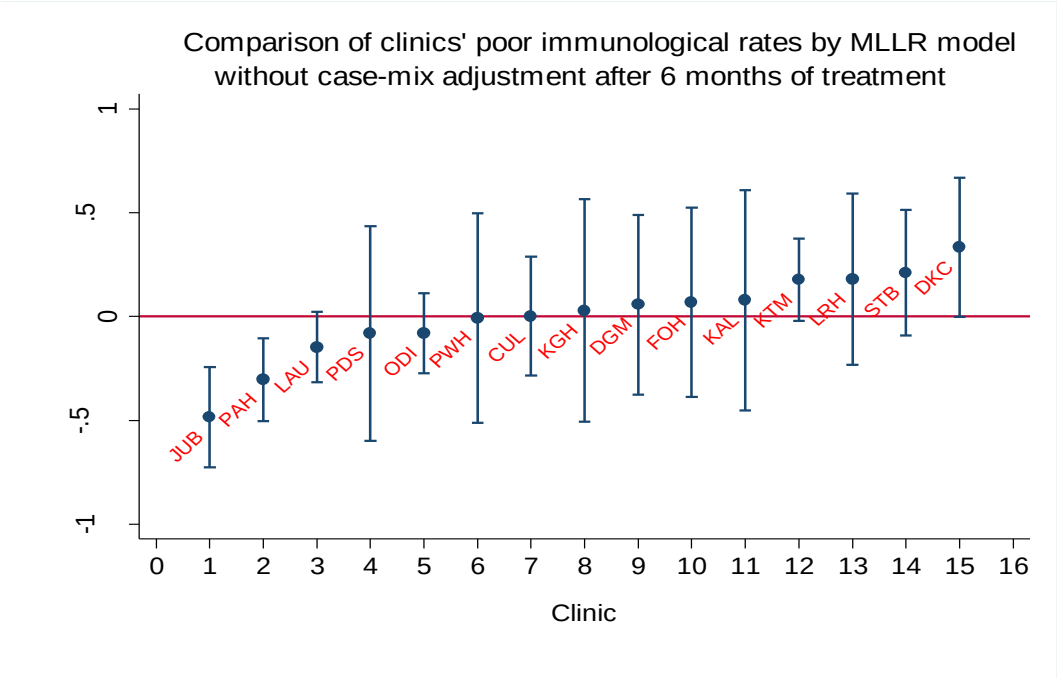

Figure 2: MLLR unadjusted RE of poor immunological outcome by clinics: 6 months

The estimate of clinics variability in the case-mix unadjusted MLLR model was 0.08, which gave an estimated intraclass coefficient (ICC) of 0.02, which implies that only a paltry 2% in the variability of poor immunological response rates between the clinics can be explained by differences within them.

4.2.4 Case-mix Odds ratios of poor immunological outcome: 6 months

Model estimates for the odds ratios of the case-mix adjusters and their standard errors are similar for the three types of models (Table 9).

Table 9: The three models' (LR, LRD and MLLR) estimates: 6 months

Factor	LR		LRD		MLLR	
	OR (SE)	p value	OR (SE)	p value	OR (SE)	p value
Age vs. 13-30 yrs						
31-45	1.33 (0.149)	0.012	1.35 (0.152)	0.009	1.34 (0.150)	0.011
46-72	1.53 (0.213)	0.002	1.56 (0.219)	0.002	1.56 (0.216)	0.002
Sex (male)	1.62 (0.150)	0.000	1.60 (0.149)	0.000	1.61 (0.149)	0.000
Regimen vs. d4T						
AZT/ZDV based	1.86 (0.320)	0.000	1.87 (0.350)	0.000	1.86 (0.324)	0.000
TDF based	0.91 (0.142)	0.525	0.81 (0.135)	0.208	0.86 (0.139)	0.366
Religion (Christian)	1.69 (0.165)	0.000	1.39 (0.165)	0.005	1.56 (0.187)	0.000
VL status (poor)	2.29 (0.290)	0.000	2.31 (0.295)	0.000	2.31 (0.292)	0.000
Area under ROC curve	0.63		0.65			
Random-effects (clinics)					**Estimate (SE)**	
					0.025 (0.026)	

The Hosmer-Lemeshow statistic (4.07, pr=0.6671) with 8 groupings indicated no lack of fit for the data by logistic regression model. The respective areas under the Receiver Operating Characteristic (ROC) for both the LR and LRD models are 0.63 and 0.65. The likelihood ratio test statistic (chi2(14) = 23.43, p =0.0536) comparing the two logistic models indicate that the model with indicators for clinics is marginally significant indicating that there could be differences in immunological response rates between the clinics after adjusting for joint confounding factors.

4.2.5 Poor immunological rates by clinic and case-mix: 6 months

Only in two clinics LAU and ODI was there a significant difference in the predicted marginal rate of poor immunological outcome between females and males (no overlapping in confidence level bands for females and males).

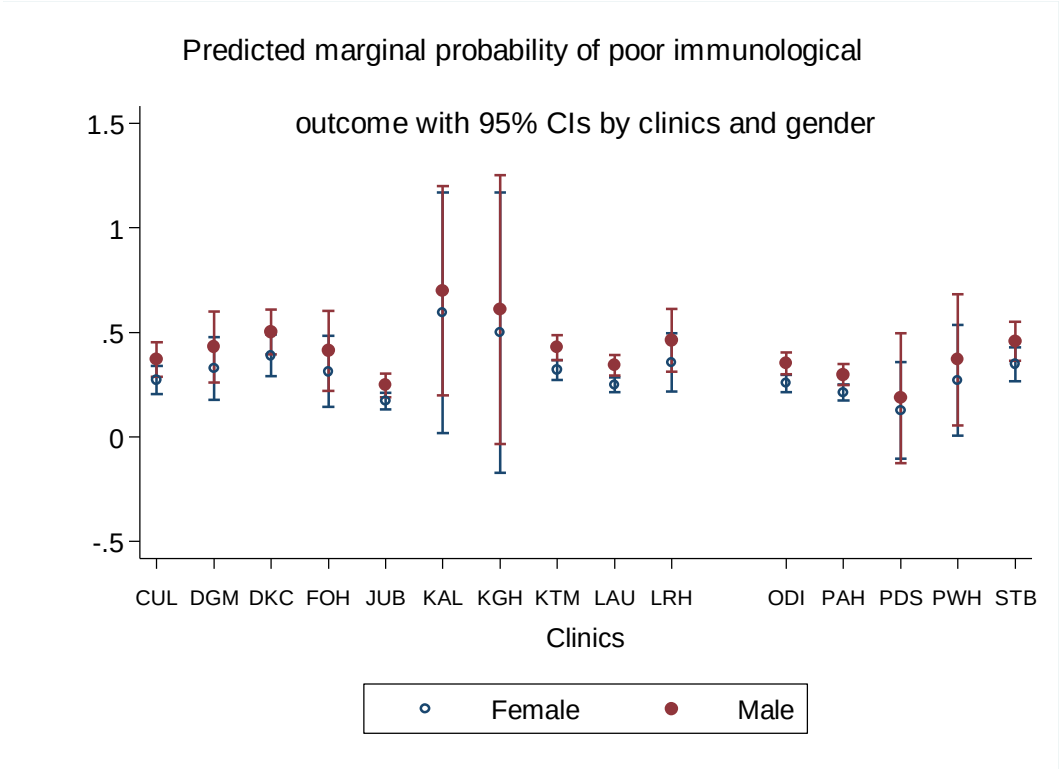

Figure 3: Poor immunological response rate by clinic and gender: 6 months

No clinic had significant difference in poor immunological rates between the three age categories, but the point estimates of poor immunological outcome increased with age for all clinics.

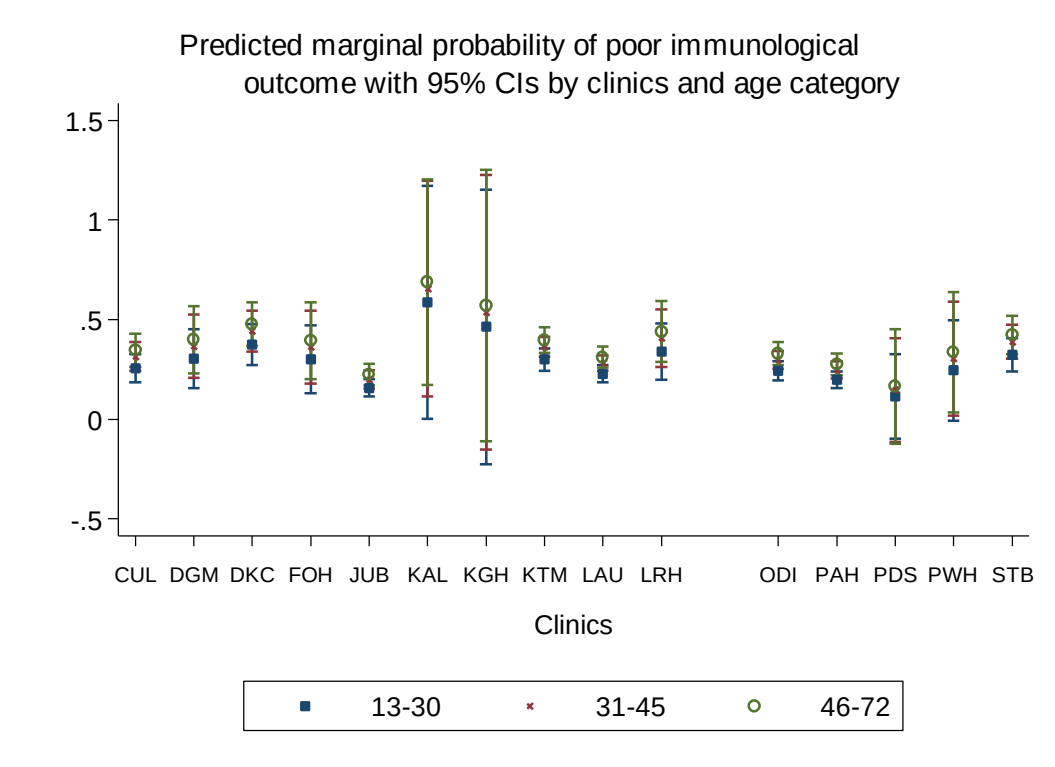

Figure 4: Poor immunological response rate by clinic and age: 6 months

No clinic had difference in poor immunological response between the two religious groups.

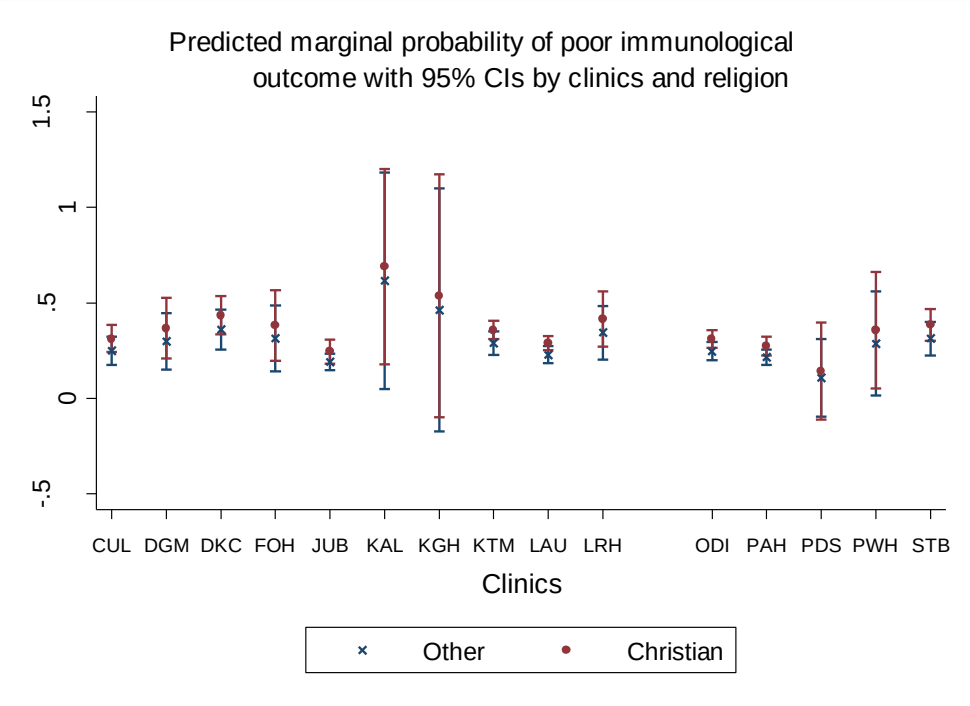

Figure 5: Poor immunological response rate by clinic and religion: 6 months

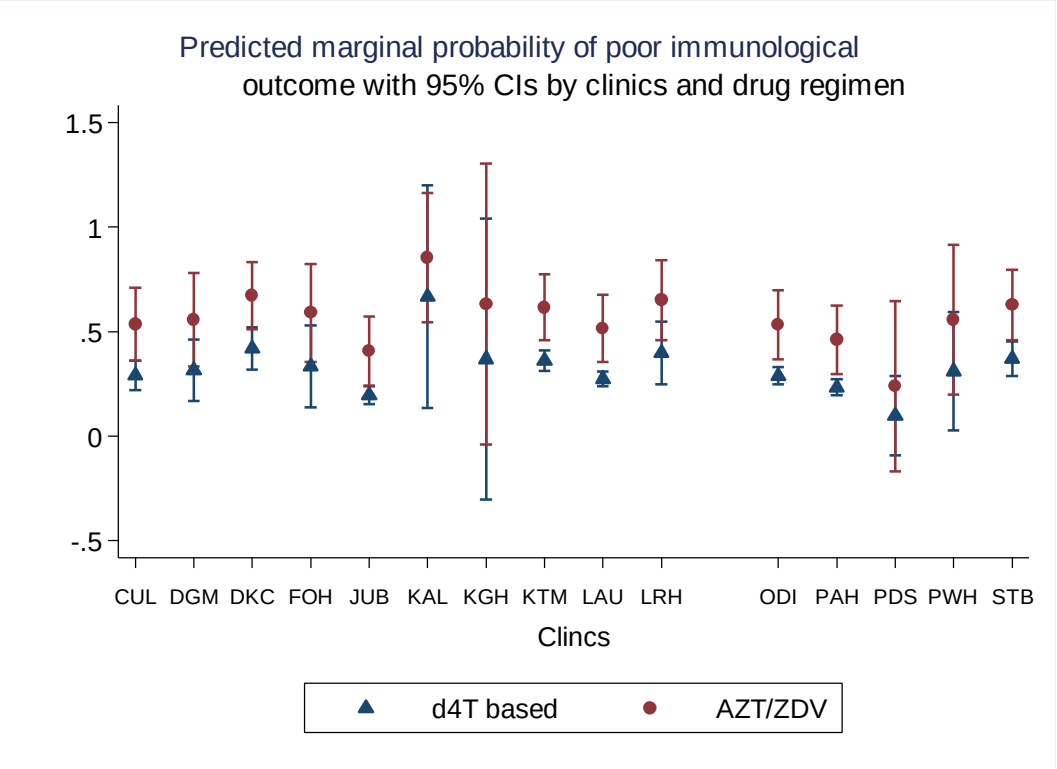

Figure 6: Poor immunological response rate by clinic and regimen (d4T vs. AZT): 6 months

There are clear significant differences in the rates of poor immunological response between patients on AZT based regimen and those of d4T and TDF based regimens (Figure 6 and Figure 7) for most of the clinics.

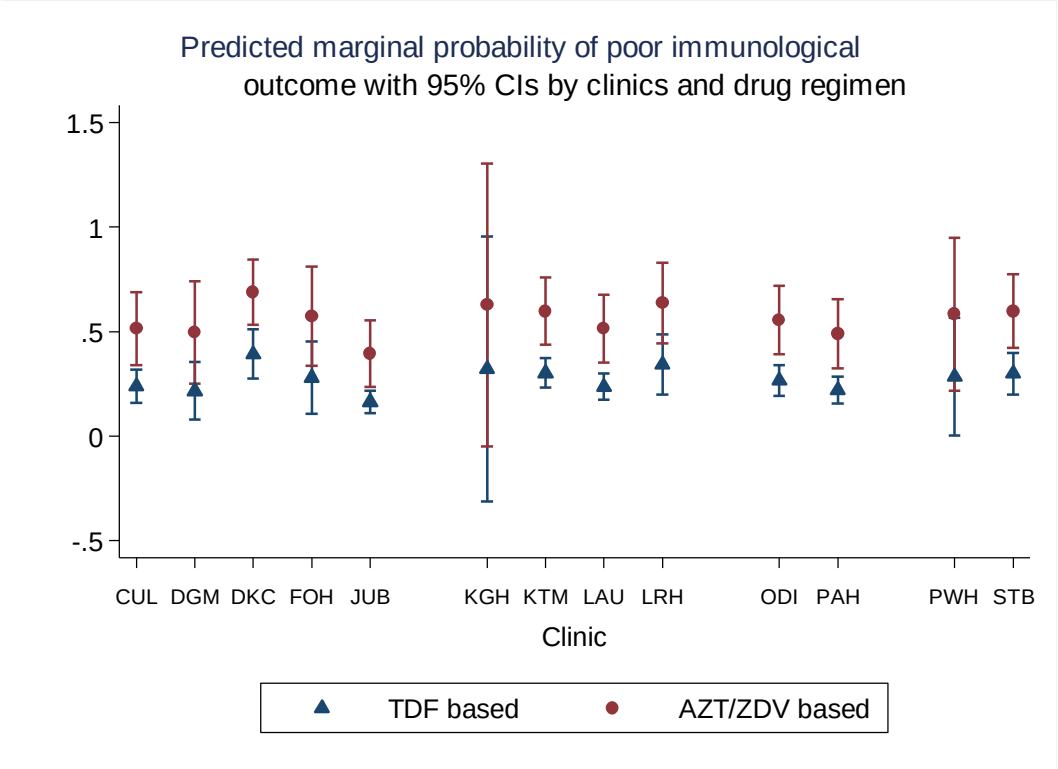

Figure 7: Poor immunological response rate by clinic and regimen (TDF vs. AZT): 6 months

4.2.6 Poor immunological rates (case-mix adjusted): 6 months

The two types of models (LR&LRD) and MLLR are now used to compare poor immunological outcome rates by clinics after case-mix adjustment.

4.2.6.1 Ordinary logistic regression (LR) model

After model adjustment, the LR model showed no clinic with a SIR that was significantly below 1 (no clinic had a SIR for which the upper value of the confidence interval was below 1), but two clinics (KTM and DKC) still had SIR that were significantly above 1. However, after case-mix adjustment, no clinic had poor immunological response rate that was significantly different from each other (confidence intervals overlap and also as indicated by likelihood ratio statistic on Table 10) unlike when there was no case-mix adjustment (Figure 1). Nevertheless, as evidenced by the confidence intervals (Figure 1 and Figure 8), the estimates for PDS, PWH, KGH and KAL may not be reliable since the sample sizes from these four clinics are small (<30).

Table 10: Case-mix adjusted LRT statistic for clinic effects: 6 months

Model	Likelihood ratio statistic, prob.
LRD vs. LR	chi(14)=23.43, pr=0.0536
MLLR vs. LR	chibar(01)=1.92, pr=0.0831

After case-mix adjustment, the clinic effects are no longer significant (Table 10), contrary to what was shown by results from the case-mix unadjusted models.

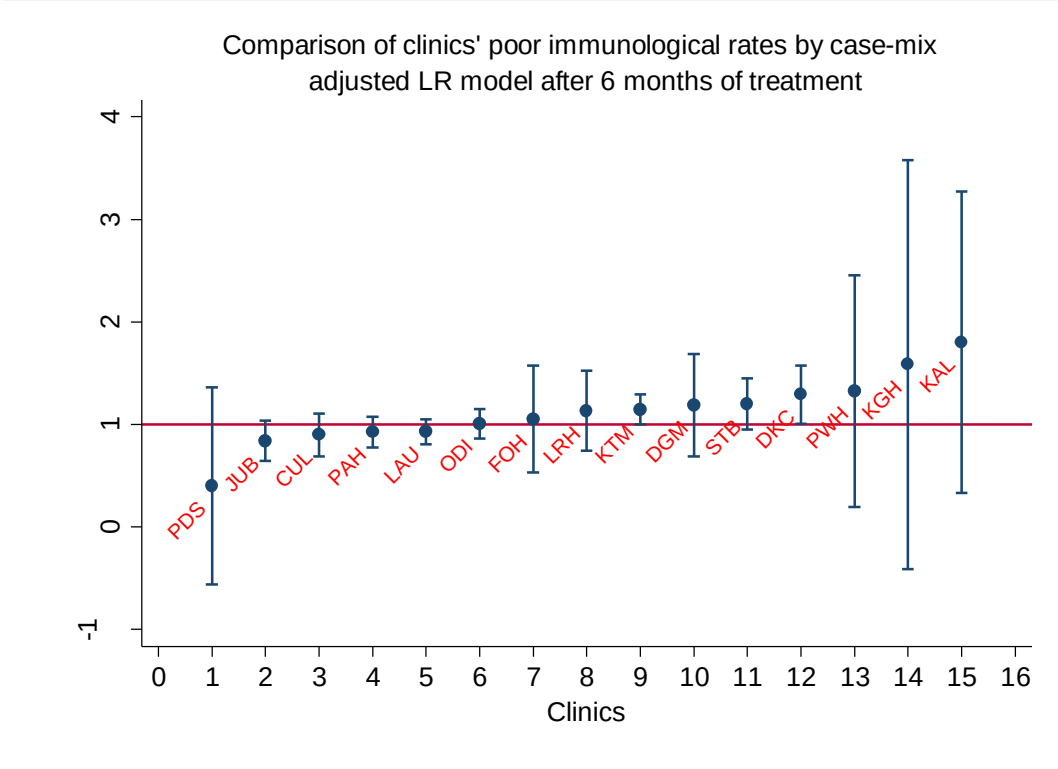

Figure 8: LR adjusted SIRs of poor immunological outcome by clinics: 6 months

4.2.6.2 Multilevel logistic regression (MLLR) model

After adjusting for case-mix in the MLLR model, there were no outlying clinics either above or below zero, neither was there any clinic that was significantly different from each other (as shown by confidence intervals) in the SIR of poor immunological response (Figure 9). The likelihood ratio statistic (1.92, pr=0.0831: Table 10) show that there is a marginal effect provided by adding an assumed unobserved/unmeasured clinic specific effect.

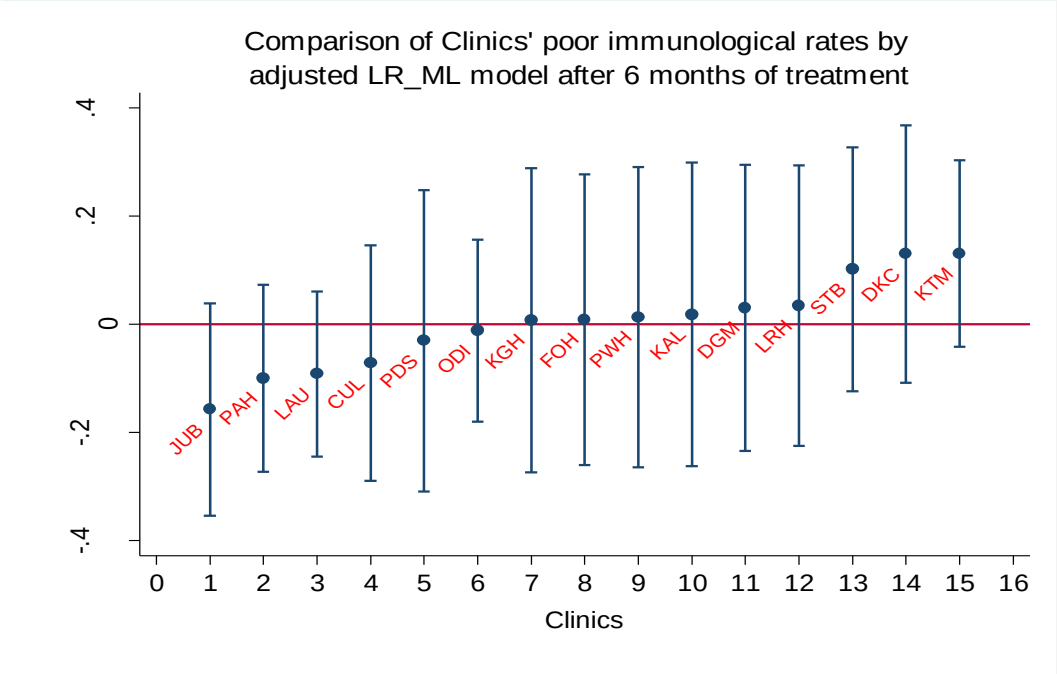

Figure 9: MLLR adjusted RE of poor immunological outcome by clinics: 6 months

The estimate of clinics variability in the case-mix adjusted MLLR model was 0.02 (much smaller than that in the unadjusted MLLR model), which gave an estimated intraclass coefficient (ICC) of 0.006, which implies that only a paltry 0.6% in the variability of poor immunological response rates between the clinics can be explained by differences within them.

4.2.7 Poor immunological rates (case-mix unadjusted): 12 months

This section reports the analysis after 12 months of treatment for the case-mix unadjusted models.

4.2.7.1 Ordinary logistic regression (LR) model

The LR model without case-mix adjustment identified three clinics (PAH, LAU and KTM) with fewer observed cases (SIR <1) of poor immunological responders than expected if there were no differences in the response rates between the clinics. Four clinics (ODI, DGM, DKC and PDS) were identified as the clinics with SIRs that were significantly above the total sample average.

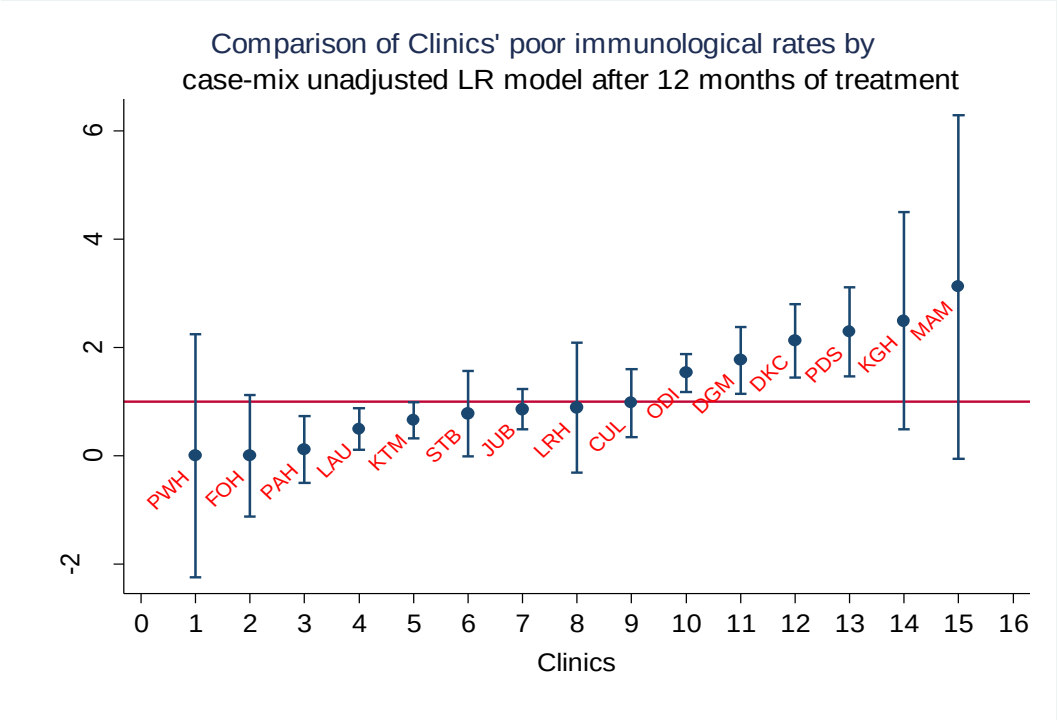

Figure 10: LR unadjusted SIRs of poor immunological outcome by clinics: 12 months

As the confidence interval shows (a number of them do not overlap), there is quite a number of clinics that have significant differences in the rates of poor immunological responses between them. For example, PAH (with lowest unadjusted rate) and LAU have poor immunological SIRs that are much lower than those of ODI, DGM, DKC and PDS.

4.2.7.2 Multilevel logistic regression (MLLR) model

The case-mix unadjusted multilevel logistic regression (MLLR) model identified two clinics (PAH and LAU) with poor immunological response rates (clinic's random effects below zero) that were below average. The model also just like the LR model, showed that four clinics (ODI, DGM, DKC and PDS) had random effects that were significantly above zero after 12 months of treatment (Figure 11).

The likelihood ratio test (chibar(01)=26.53, pr=0.000) between LR and MLLR models show that the MLLR model is necessary and there are significant unmeasured/unobserved clinic specific effects. The intraclass correlation

coefficient ICC=0.14) indicate that approximately 14% of the variability in poor immunological outcome is attributable to differences between clinics.

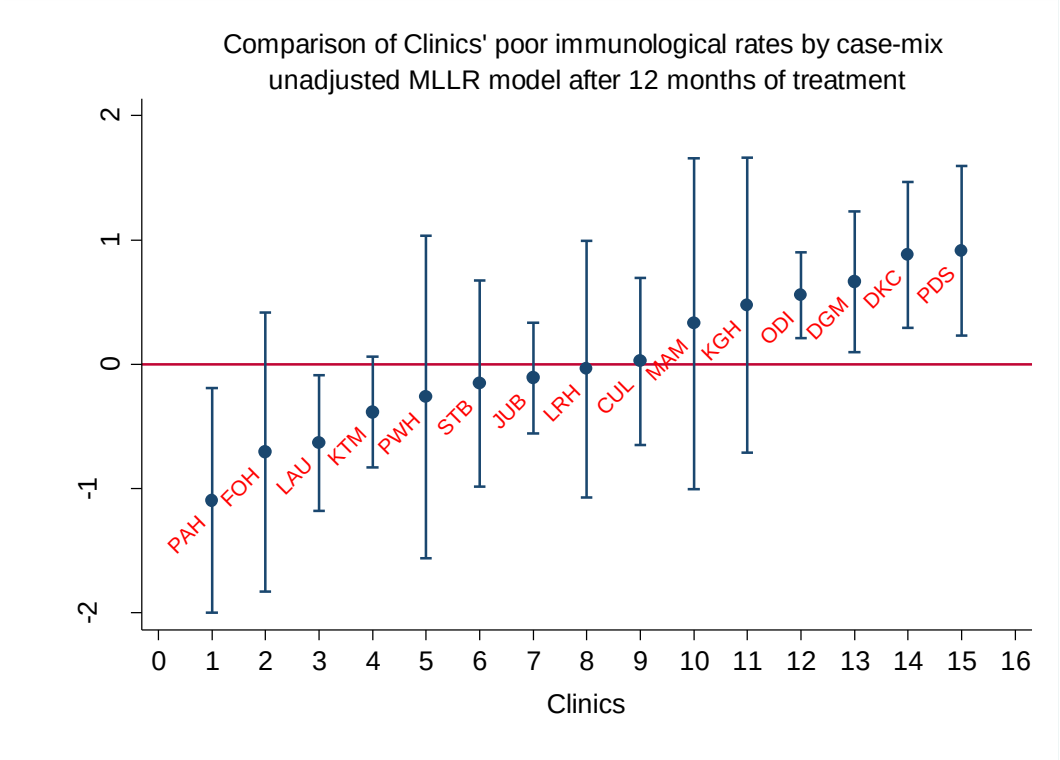

Figure 11: MLLR unadjusted RE of poor immunological outcome by clinics: 12 months

4.2.8 Poor immunological rates (case-mix adjusted): 12 months

Unlike after 6 months of treatment where the estimates for the odds ratios were similar, the estimates for odds ratios of some case-mix adjusters differ marginally between the three types of models after 12 months of treatment.

The odds ratio of poor immunological outcome for gender (male), baseline age (46-72 years) and drug (AZT/ZDV based) are higher after 12 months of treatment than after 6 months of treatment, while those of religion and virological status drop after 12 months of treatment compared with those after 6 months of treatment. The clinic effects are quite profound after 12 months of treatment for both the case-mix unadjusted and adjusted models.

The Hosmer-Lemeshow statistic (3.73, pr=0.4437) with 6 groupings indicated no lack of fit for the data by the logistic regression model. The respective areas

under the Receiver Operating Characteristic (ROC) for both the LR and LRD models are 0.66 and 0.74 (also higher than those got after 6 months of treatment). The likelihood ratio test statistic (chi2 (14) = 57.20, pr=0.0000: Table 12) comparing the two logistic models indicate that the model with indicators for clinics is necessary (shows that there are unmeasured/unobserved clinic factors that may account for observed immunological response rates differences between the clinics, after adjusting for other known confounding factors).

Table 11: The three models' (LR, LR-D and MLLR) estimates: 12 months

Effect	LR		LRD		MLLR	
	OR (SE)	p value	OR (SE)	p value	OR (SE)	p value
Age vs. 13-30 yrs						
31-45	1.10 (0.281)	0.720	1.00 (0.265)	0.996	1.01 (0.266)	0.966
46-72	2.08 (0.595)	0.010	1.79 (0.538)	0.054	1.86 (0.552)	0.036
Sex (male)	2.29 (0.439)	0.000	2.47 (0.502)	0.000	2.36 (0.471)	0.000
Regimen vs. d4T						
AZT/ZDV based	2.38 (0.656)	0.002	2.28 (0.696)	0.007	2.25(0.668)	0.006
TDF based	1.23 (0.332)	0.945	1.23 (0.438)	0.555	1.13 (0.388)	0.709
Religion (Christian)	1.35 (0.275)	0.141	1.43 (0.413)	0.209	1.50 (0.399)	0.129
VL status (poor)	1.89 (0.470)	0.011	1.82 (0.469)	0.021	1.83 (0.468)	0.019
Area under ROC curve	0.66		0.74			
Random-effects (clinics)					**Estimate (SE)**	
					0.51 (0.330)	

In both the case-mix unadjusted and adjusted models, the likelihood ratio test shows that the models that account for differences in the clinics (LRD and MLLR) are preferable over the model (LR) that does not take into account the unmeasured clinic effects (Table 12), although the respective chi square statistics drop between the two kinds of models (case-mix adjusted and unadjusted.)

Table 12: LRT statistic to test for clinic effects after 12 months of treatment

Model		Likelihood ratio statistic, prob.
Unadjusted	LRD vs. LR	chi(14)=64.36, pr=0.0000
	MLLR vs. LR	chibar(01)=26.53, pr=0.0000
Adjusted	LRD vs. LR	chi(14)=57.20, pr=0.0000
	MLLR vs. LR	chibar(01)=21.22, pr=0.000

The adjusted LR model identified four clinics (FOH, PAH, LAU and KTM) with SIR below 1, and four clinics (ODI, DGM, DKC and PDS) with SIR above 1.

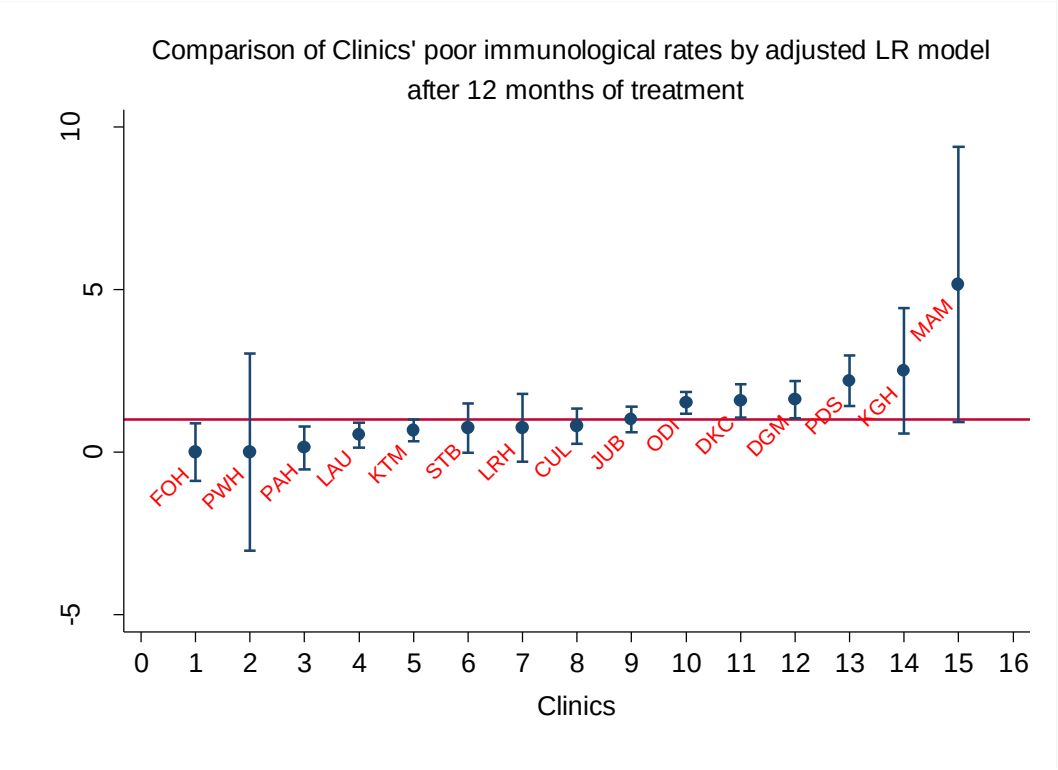

Figure 12: LR adjusted SIRs of poor immunological outcome by clinics: 12 months

On the other hand, the adjusted MLLR model showed the same four clinics with random effects above zero, but marginally flagged only two clinics (PAH and LAU) as having random effects below zero.

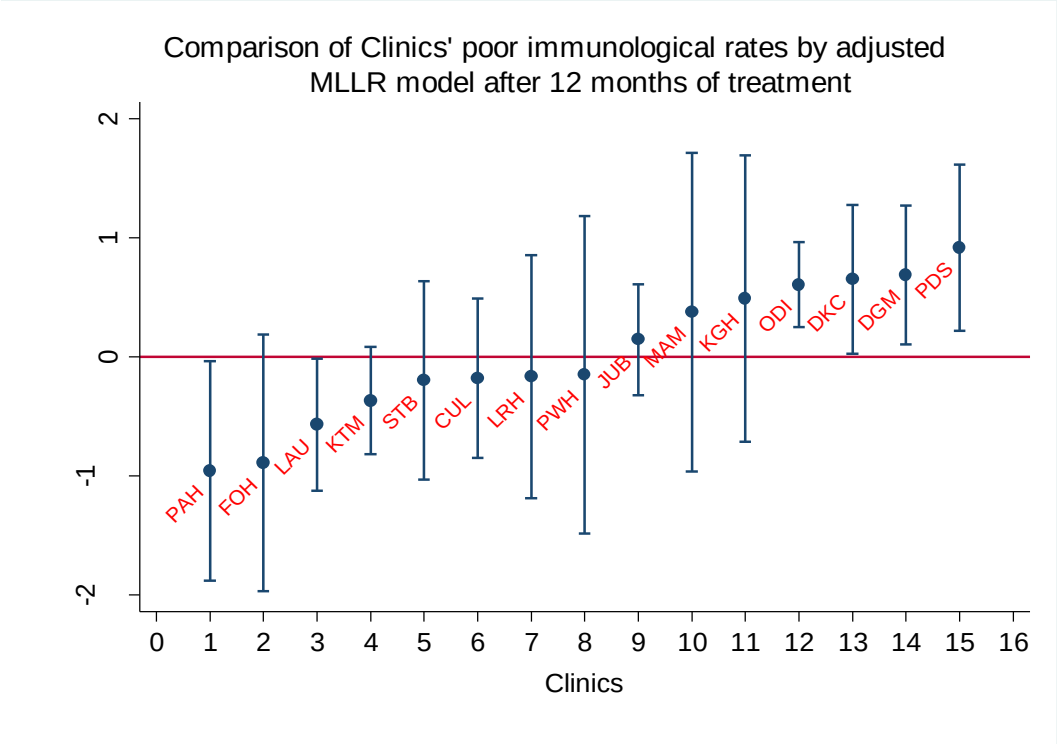

Figure 13: MLLR adjusted RE of poor immunological outcome by clinics: 12 months

4.2.9 Effect of case-mix adjustment on clinics' comparison results by model type (LR and MLLR): 6 months

The following results show how the order of the clinics' poor immunological rates differ before and after case-mix adjustment for both the ordinary logistic regression (LR) and multilevel logistic regression (MLLR) models.

4.2.9.1 Logistic regression (LR)

The scatter plot (Figure 14) indicate that the Standardised Incidence Ratio (SIR) of poor immunological response for CUL dropped substantially below that of PAH, LAU and ODI, as was that of LRH which dropped below those of DGM, KTM and STB after case-mix adjustment. The SIR of FOH also dropped below that of DGM and KTM

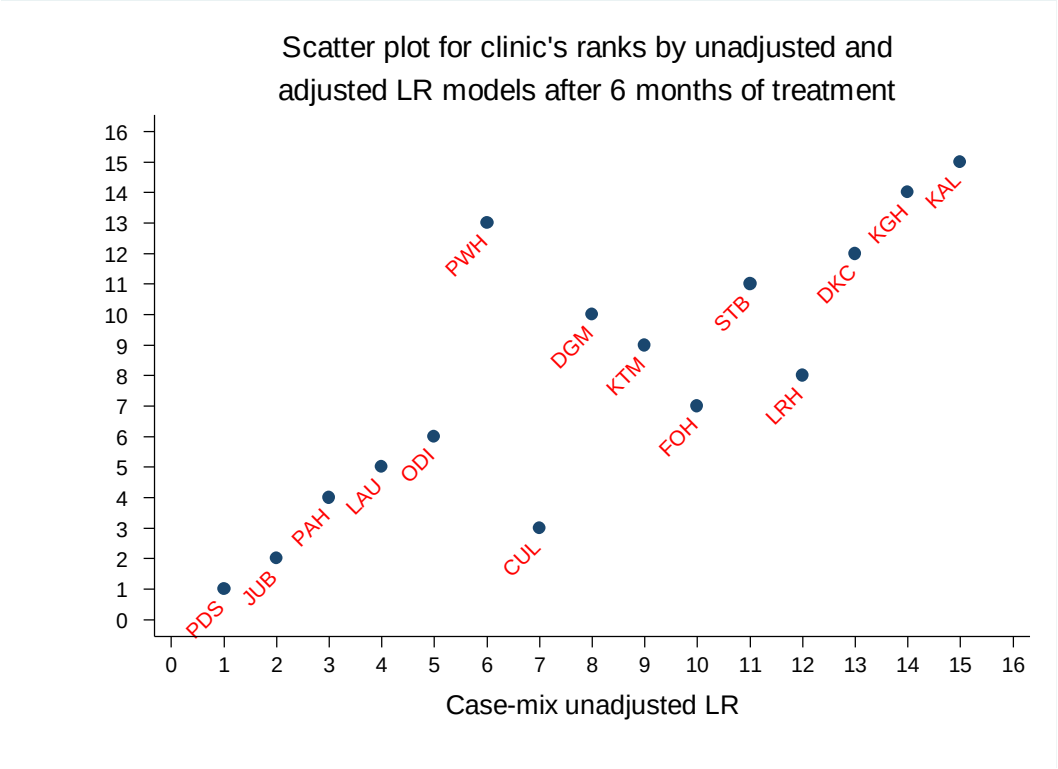

Figure 14: ART provider ranking by unadjusted and adjusted LR model: 6 months

There is some discrepancy between the clinics' ordered SIRs for the case-mix unadjusted and case-mix adjusted LR models as shown by the correlation coefficient of 0.83 (Table 13). This discrepancy represents changes in the SIRs brought about by the case-mix adjustment and is what can be attributed to differences in the patients' composition between the clinics. It indicates that some of the clinics' SIR for poor immunological outcome increased or decreased relative to each other after case-mix adjustment. The increases or the decreases may not however be significant.

Table 13: Correlation coefficient matrix for ART provider rankings: 6 months

	Unadjusted LR	Adjusted LR	Unadjusted MLLR	Adjusted MLLR
Unadjusted LR	1.0000			
Adjusted LR	0.8250	1.0000		
Unadjusted MLLR	0.8429	0.6464	1.0000	
Adjusted MLLR	0.7036	0.6821	0.9250	1.0000

4.2.9.2 Multilevel Logistic regression (MLLR)

For the multilevel model, although the changes are not the same as for the LR model, case mix adjustment again affected the random effects of CUL and FOH by causing it to drop relative to that of other clinics. Clinics with small sample sizes (e.g. KAL and KGH) are not necessarily the ones with worse poor outcomes, unlike in the LR modelling.

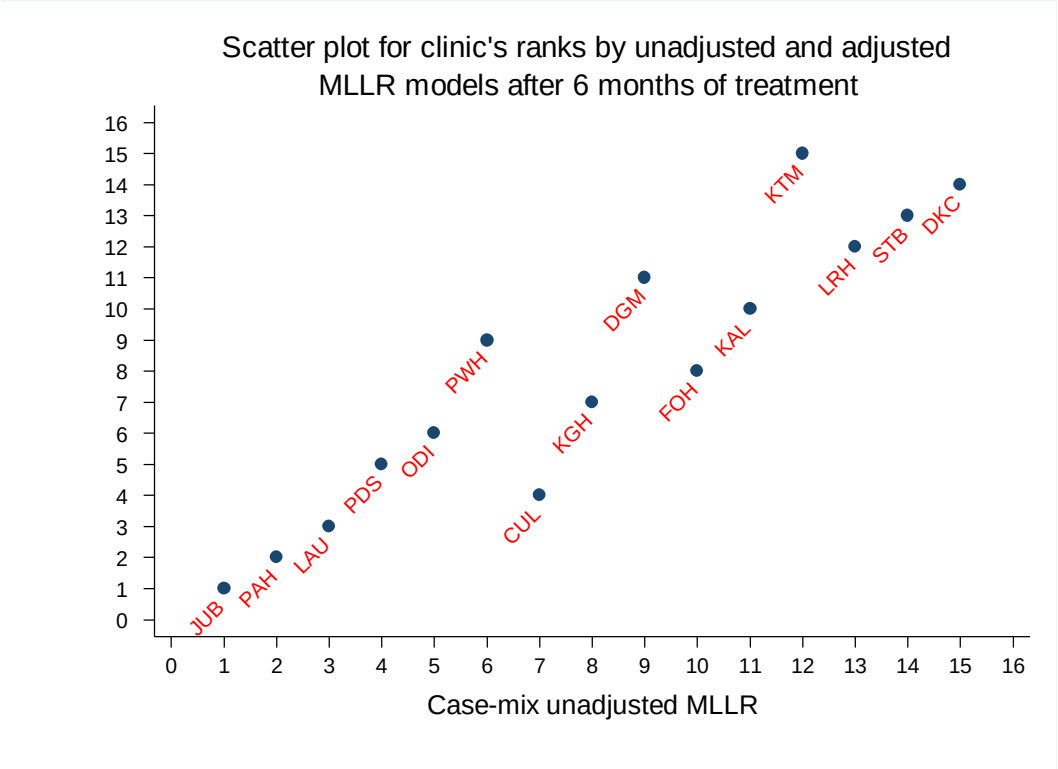

Figure 15: RE by case-mix unadjusted and adjusted MLLR model: 6 months

The correlation coefficient between clinics' order of the random effects of poor immunological outcome by the case-mix unadjusted and adjusted MLLR models is 0.93.

4.2.10 Effect of type of model (LR or MLLR) on clinics' comparison results in unadjusted and adjusted case-mix models after 6 months of treatment

The emphasis of the following results is to show how the two types of models deal with clinics with small sample sizes (e.g. PDS, KAL, KGH and PWH).

4.2.10.1 Without case-mix adjustment

The crude rates of poor immunological response rates for the three clinics are 14% (1 out of 7), 67% (2 out of 3) and 50% (1 out of 2) respectively. Thus the LR model shows that PDS has the lowest, and KGH and KAL the second highest and highest rates of poor immunological response.

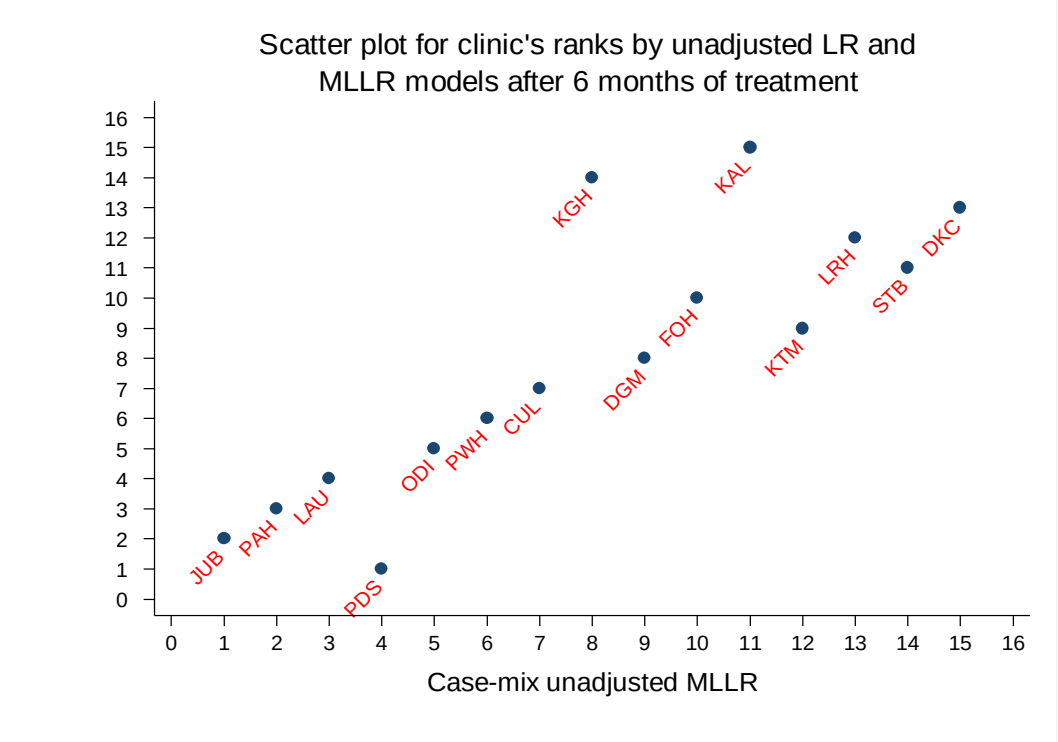

Figure 16: ART provider rankings by unadjusted LR and MLLR models: 6 months

The MLLR model unlike the LR model adjusts for estimates of the clinics with small sample size by pooling them towards the overall mean rate. The correlation coefficient of provider's ART ranking of poor immunological outcome by unadjusted LR and MLLR models is 0.84 (Table 13).

4.2.10.2 With case-mix adjustment

The correlation coefficient between the ordered SIRs by the adjusted LR and MLLR models is 0.68 (Table 13), and this disparity is high since it indicates differences due to case-mix adjustments as well as adjustments due to clinics with small sample size.

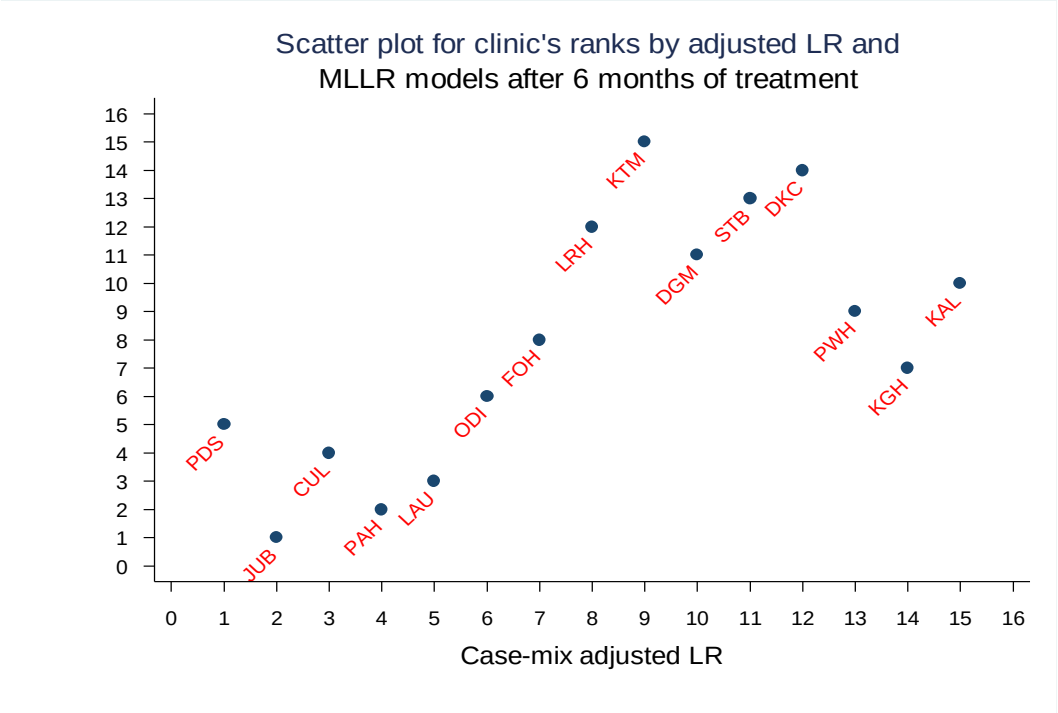

Figure 17: ART provider ranking by adjusted LR and MLLR models: 6 months

4.2.11 Effect of case-mix adjustment on clinics' comparison results by model type (LR and MLLR) after 12 months of treatment

Table 14: Correlation coefficient matrix for ART provider rankings: 12 months

	Unadjusted LR	Adjusted LR	Unadjusted MLLR	Adjusted MLLR
Unadjusted LR	1.0000			
Adjusted LR	0.9821	1.0000		
Unadjusted MLLR	0.8714	0.8679	1.0000	
Adjusted MLLR	0.7821	0.8250	0.9536	1.0000

4.2.11.1 Logistic regression (LR)

The correlation coefficient of ART provider ranking of poor immunological response by the unadjusted and adjusted LR models is 0.98, while that by the unadjusted and adjusted MLLR models is 0.95 (Table 14). This shows that very little changes occurred in the clinics' outcome rates of poor immunological response relative to each other after case-mix adjustment.

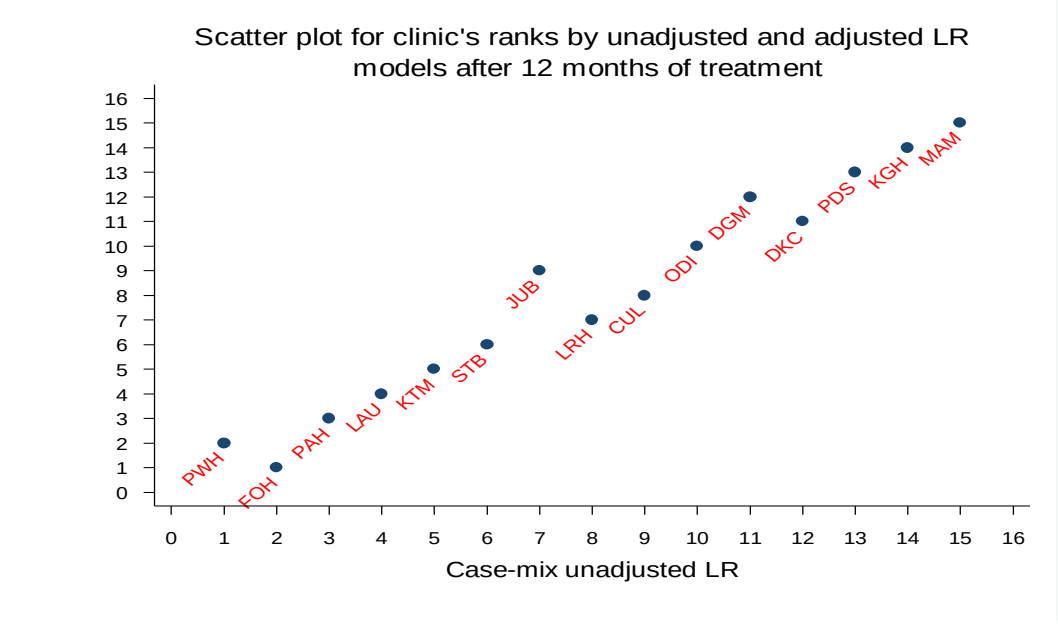

Figure 18: ART provider rankings by unadjusted and adjusted LR model: 12 months

4.2.11.2 Multilevel Logistic regression (MLLR)

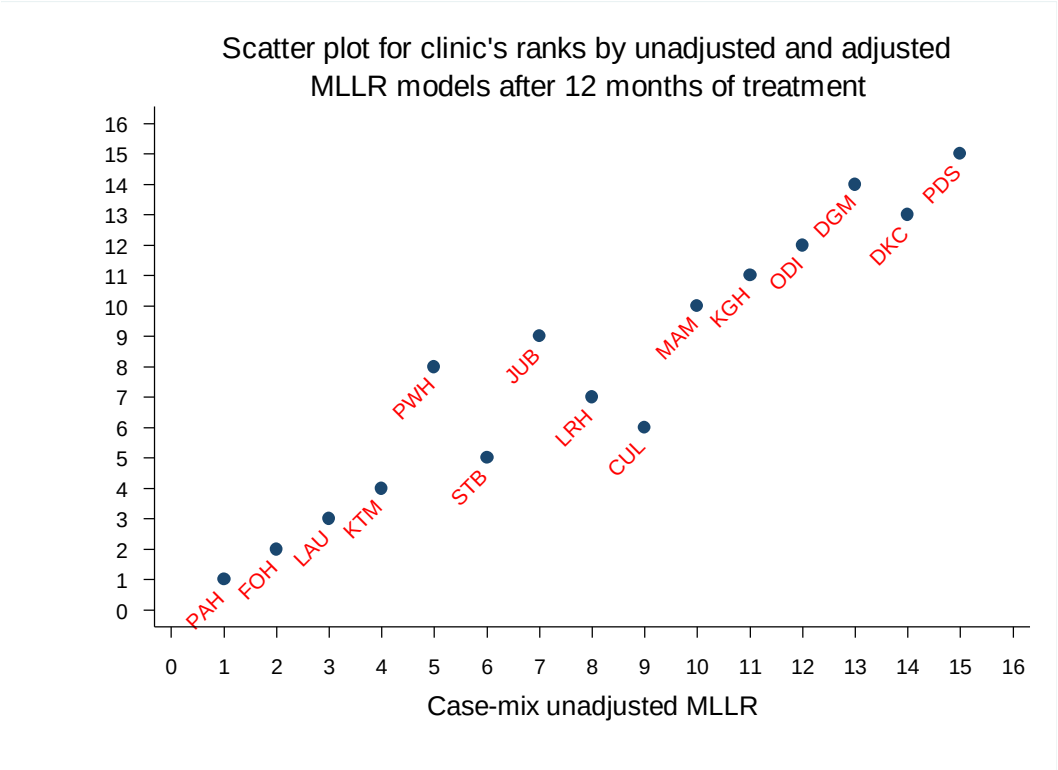

Figure 19: ART provider rankings by unadjusted and adjusted MLLR model: 12 months

4.2.12 Effect of type of model on clinics' comparison results by case-mix (without and with) status after 12 months of treatment

After 12 months of treatment, the correlation coefficient of ART provider ranking for poor immunological response by the unadjusted LR and unadjusted MLLR models is 0.87, while that by the adjusted LR and adjusted MLLR models is 0.83. This again, as in the case after 6 months of treatment reflects the way estimates by the two types of models are treated in clinics with small sample sizes. The discrepancy in the ART provider ranking of poor immunological outcome after 12 months of treatment is lower than that after 6 months of treatment.

4.2.12.1 Without case-mix adjustment

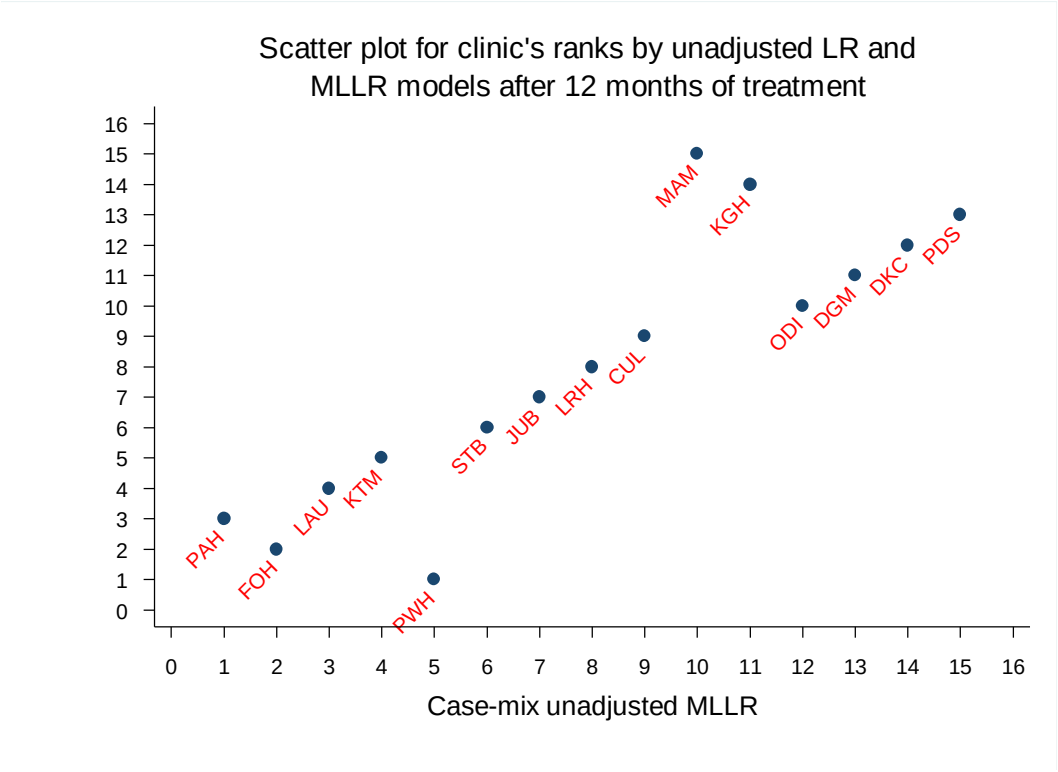

Figure 20: ART provider ranking by unadjusted LR and MLLR models: 12 months

From the scatter plot (Figure 20), it can be seen that the discrepancy is only due to the clinics with small sample sizes (PWH, KGH and MAM).

4.2.12.2 With case-mix adjustment

The difference in the ART provider ranking of poor immunological outcome between the two types of case-mix adjusted models (LR and MLLR) is due to clinics with small sample size (Figure 21). In the absence of these clinics there is almost a near agreement in the order of provider rankings.

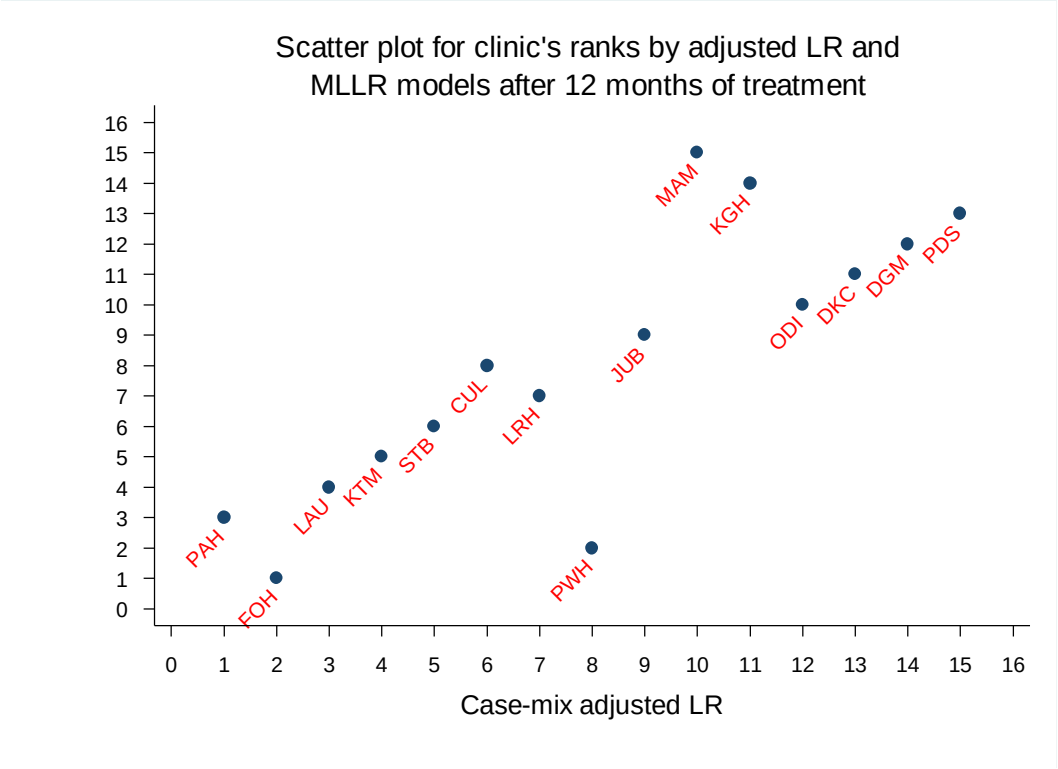

Figure 21: ART provider ranking by adjusted LR and MLLR model: 12 months

4.3 VIROLOGICAL RESPONSE

The overall (all clinics combined) percentage of poor virological response was 12% after 6 months of treatment and 13% after 12 months of treatment.

4.3.1 Virological outcome by clinic

DGM and LRH had the highest unadjusted rates (20% and 21% respectively) of poor virological outcome after 6 months of treatment, while after 12 months of treatment DGM again had the highest rate (21%) of poor virological response (Table 15). Most clinics had poor virological response rates that were close to the overall mean rate after 6 and 12 months of treatment. Of the clinics with relatively large sample sizes, PAH had the lowest percentage of poor virological response at 9% after 6 months of treatment while STB had the lowest rate (6%) after 12 months of treatment. The respective clinic's poor virological rate either dropped or increased after 12 months of treatment compared with that of after 6 months of

treatment but still remained in the neighbourhood of the overall rate (13%) of poor virological response (Table 15).

Table 15: Virological response rates by clinics

Clinic	6 Months			12 Months		
	Good	Poor	Total	Good	Poor	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
CUL	137 (87%)	21 (13%)	158 (100%)	46 (90%)	5 (10%)	51 (100%)
DGM	28 (80%)	7 (20%)	35 (100%)	42 (79%)	11 (21%)	53 (100%)
DKC	81 (90%)	9 (10%)	90 (100%)	37 (84%)	7 (16%)	44 (100%)
FOH	24 (96%)	1 (4%)	25 (100%)	16 (100%)	0 (0%)	16 (100%)
JUB	270 (87%)	41 (13%)	311 (100%)	127 (88%)	18 (12%)	145 (100%)
KAL	2 (67%)	1 (33%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)
KGH	2 (100%)	0 (0%)	2 (100%)	5 (100%)	0 (0%)	5 (100%)
KTM	335 (89%)	40 (11%)	375 (100%)	157 (87%)	23 (13%)	180 (100%)
LAU	531 (88%)	71 (12%)	602 (100%)	122 (88%)	17 (12%)	139 (100%)
LRH	33 (79%)	9 (21%)	42 (100%)	13 (93%)	1 (7%)	14 (100%)
MAM	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)
ODI	392 (89%)	49 (11%)	441 (100%)	139 (83%)	28 (17%)	167 (100%)
PAH	408 (91%)	42 (9%)	450 (100%)	44 (83%)	9 (17%)	53 (100%)
PDS	6 (86%)	1 (14%)	7 (100%)	28 (93%)	2 (7%)	30 (100%)
PWH	9 (90%)	1 (10%)	10 (100%)	4 (100%)	0 (0%)	4 (100%)
STB	110 (87%)	17 (13%)	127 (100%)	30 (94%)	2 (6%)	32 (100%)
Total	**2368 (88%)**	**310 (12%)**	**2678 (100%)**	**812 (87%)**	**123 (13%)**	**935 (100%)**

4.3.2 Univariate Analysis

The univariate analysis identified CD4 count and age to be the only case-mix adjusters that were associated with poor virological outcome after both 6 and 12 months of treatment.

Table 16: Case-mix odds ratios of poor virological outcome (univariate analysis)

Factor	6 months			12 months		
	Odds Ratio	Pr	95% CI	Odds Ratio	Pr	95% CI
Baseline CD4 count	0.997	0.006	0.996-0.999	0.999	0.002	0.997 – 1.000
Age (vs. 46-72 yrs)						
13-30	1.95	0.001	1.33 – 2.89	1.97	0.018	1.12 – 3.45
31-45	1.42	0.052	0.996 – 2.03	0.87	0.612	0.51 – 1.48
Marital status (vs. Single)						
Married	0.81	0.153	0.60 - 1.08	1.08	0.731	0.69 - 1.69
Divorced/Widowed	0.70	0.232	0.39- 1.26	0.72	0.460	0.30 - 1.72

The odds of virological failure decrease by a paltry less than 1% for every 1 measurement increase in CD4 count. A 50 point increase in CD4 count would be associated with an odds ratio of about exp(50×ln (0.997) = 0.86 or 14% decrease in the odds of poor virological response.

Table 17: Clinics' OR of poor virological response: 6 months

Clinic	Unadjusted odds ratios				Adjusted odds ratios		
	N	*OR*	*Prob.*	*95% CI*	*OR*	*Prob.*	*95% CI*
CUL	158	1.5	0.162	(0.9, 2.6)	1.6	0.124	(0.9, 2.7)
DGM	35	2.4	0.05	(1.0, 5.9)	2.0	0.13	(0.8, 5)
DKC	90	1.1	0.844	(0.5, 2.3)	1.0	0.906	(0.4, 2.1)
FOH	25	0.4	0.381	(0.1, 3.1)	0.4	0.367	(0.1, 3)
JUB	311	1.5	0.095	(0.9, 2.3)	1.6	0.061	(1, 2.5)
KAL	3	4.9	0.201	(0.4, 54.7)	4.1	0.251	(0.4, 46.8)
KGH	2	1			1.0		
KTM	375	1.2	0.524	(0.7, 1.8)	1.1	0.82	(0.7, 1.7)
LAU	602	1.3	0.203	(0.9, 1.9)	1.3	0.223	(0.9, 1.9)
LRH	42	2.6	0.017	(1.2, 5.9)	2.5	0.026	(1.1, 5.8)
MAM	-		-	-			
ODI	441	1.2	0.381	(0.8, 1.9)	1.1	0.579	(0.7, 1.8)
PAH	450	1	-	-	1.0	-	-
PDS	7	1.6	0.659	(0.2, 13.8)	1.9	0.572	(0.2, 16)
PWH	10	1.1	0.943	(0.1, 8.7)	1.1	0.903	(0.1, 9.3)
STB	127	1.5	0.185	(0.8, 2.7)	1.4	0.296	(0.8, 2.5)

As shown on Table 17, the unadjusted and adjusted odds ratios for clinics' poor virological outcome rates are almost the same. This implies that case-mix adjustment affected the poor virological response rate between the clinics minimally.

4.3.3 Comparison of clinics' SIR of poor virological outcome by case-mix unadjusted LR model after 6 months of treatment

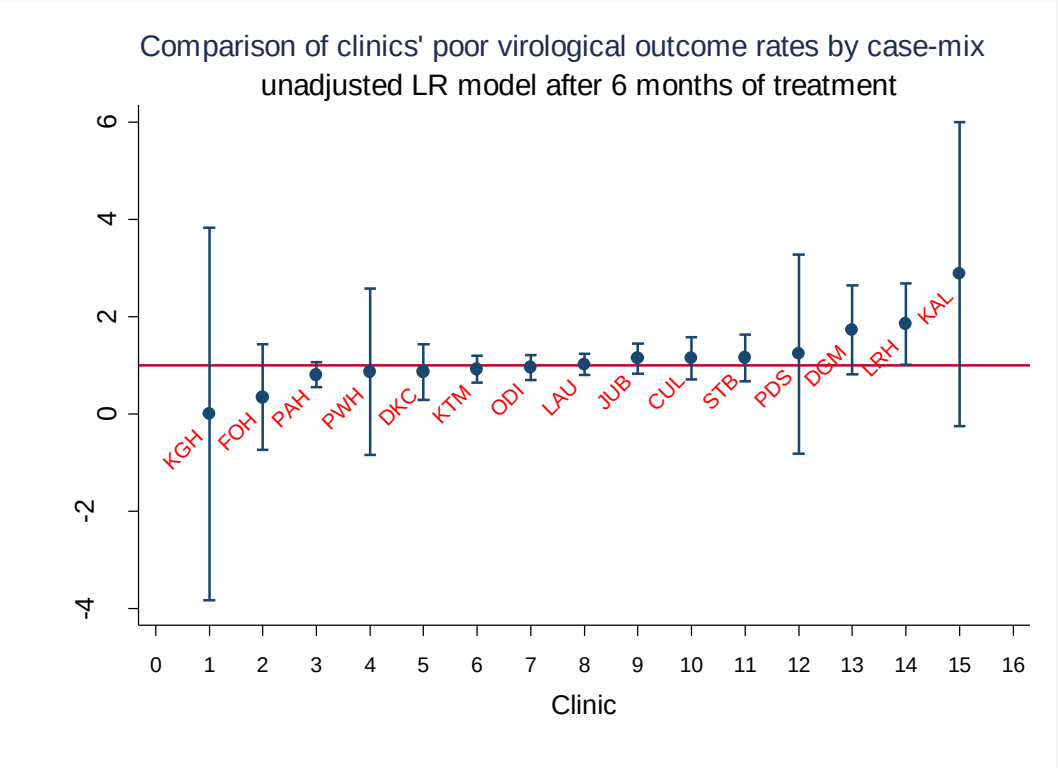

Figure 22: Unadjusted virological response rates by clinics: 6 months

LRH is the only clinic that seems to be having more than expected number of virological poor outcome. This clinic's SIR also appears to be almost different from that of PAH (Figure 22).

4.3.4 Comparison of clinics' SIR of poor virological outcome by case-mix adjusted LR model after 6 months of treatment

The Hosmer-Lemeshow statistic (chi2(8)=17.96, Pr=0.0215) shows that this model is not a good fit. The model's discriminative ability is also poor; area under curve (AUC) of the receiver operating characteristic (ROC) is 0.62. This could be

as a result of necessary covariates being unavailable for model adjustment. However, even under these circumstances and after adjusting for the two factors of age and CD4 count, there is no clinic that has more observed cases of poor virological responders than would be expected under the assumption of equal poor virological outcome rates between the clinics. There is also no clinic that had a poor virological response rate that was significantly different from other clinics.

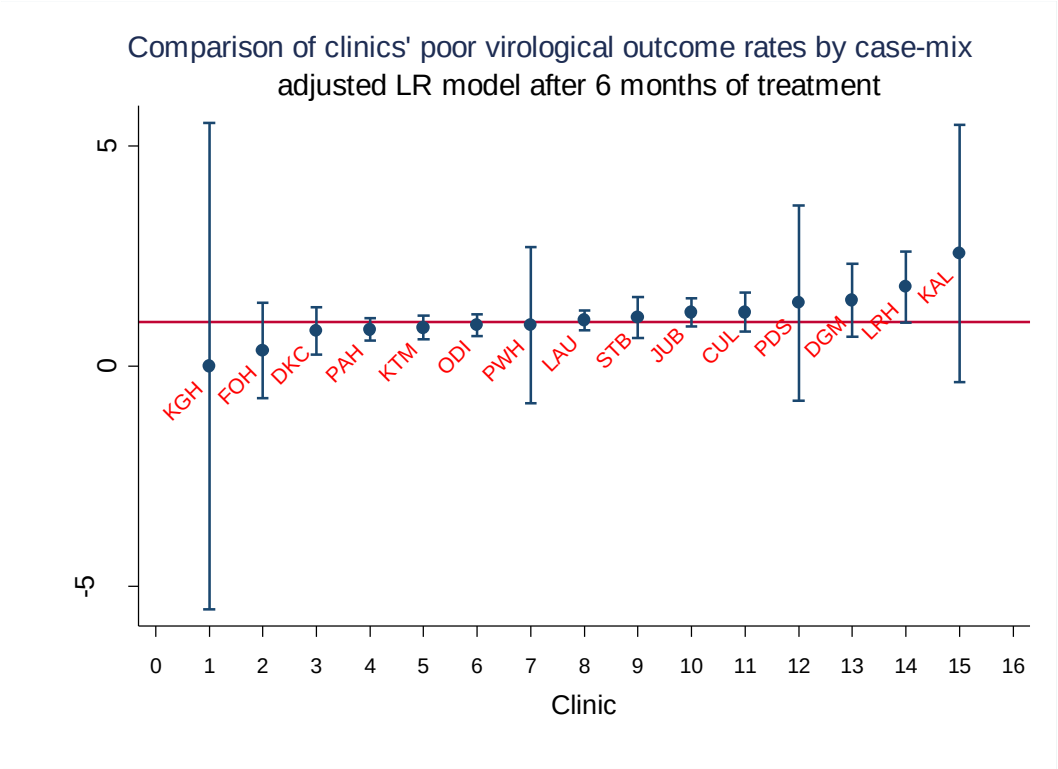

Figure 23: Adjusted virological response rates by clinics: 6 months treatment

The model with indicator variable for clinics (LRD) was not significant compared with the LR model (Likelihood ratio test, chi2(13) = 13.51, Pr = 0.4090), neither was also the ML model necessary (Likelihood ratio test vs. logistic regression: chibar2(01) = 0.00, Pr. = 1.0000). These two latter models indicate there were no clinic effects that could explain differences in poor virological response. As can be seen from both Figure 22 and Figure 23, the virological response rate for more than 8 clinics was almost equal to the overall rate (12%) or a ratio of 1.

The correlation coefficient for ranks by the null logistic model and by the adjusted logistic regression model is 0.98, showing very minimal changes after case mix adjustment.

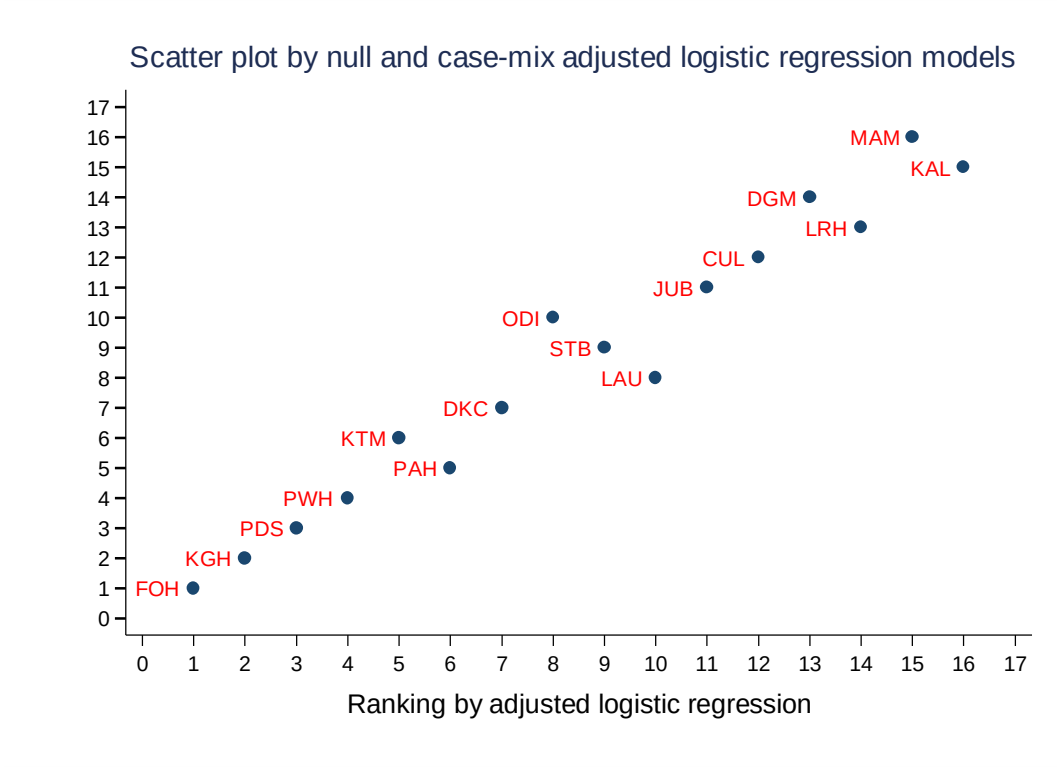

Figure 24: Scatter plot of ranking by null and adjusted logistic regression

4.3.5 Poor virological outcome (case-mix adjusted): 12 months

The Hosmer-Lemeshow statistic (chi2(8)=10.22, Pr=0.2501) shows no evidence of lack of fit in this model. The model's discriminative ability is rather poor as area under curve (AUC) of the receiver operating characteristic (ROC) is 0.65 (slightly higher than that of analysis after 6 months of treatment). After adjusting for the age and CD4 count, there was no clinic that had a SIR of poor virological response that was higher or lower than expected under the assumption of equal poor virological outcome rates between the clinics. There was also no clinic that had a SIR of poor virological response that was significantly different from each other. The number of clinics that had SIRs that were below or equal to the average after 12 months of treatment was slightly more compared with the number of clinics after 6 months of treatment.

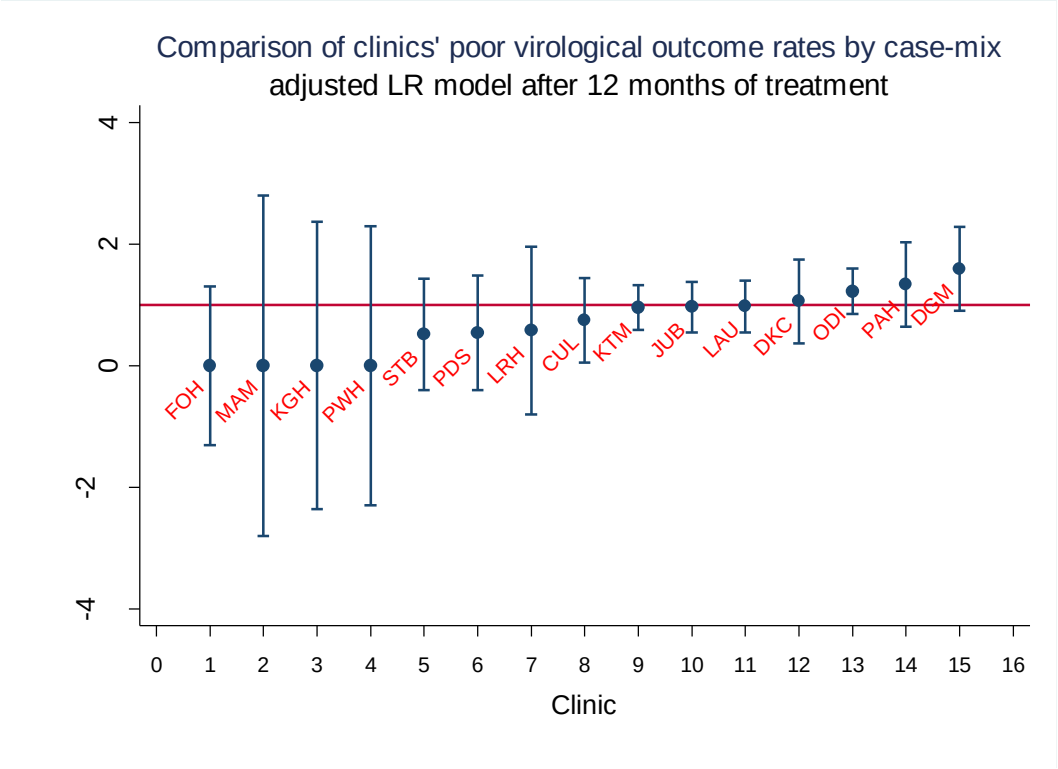

Figure 25: LR adjusted SIRs of poor virological outcome by clinics: 12 months

CHAPTER FIVE

5.1 DISCUSSION

In this study, the aim was to compare differences in poor immunological and virological outcome rates for adult and adolescent HIV positive patients on ARV for 16 clinics within Tshwane district after 6 and 12 months of treatment. Specific objectives were to 1) separately examine patient level factors that are associated with poor immunological and virological outcomes, and 2) compare the disaggregated poor immunological and virological rates between clinics, before and after case-mix adjustments. To achieve these objectives, three types of models, that is, fixed-effects logistic regression model (LR), fixed effects logistic regression model with indicators for clinics (LRD) and multilevel logistic regression model (MLLR); without and with patient-level risk factor adjustments were used for comparing differences in response rates for the two indicators between the clinics.

5.2 IMMUNOLOGICAL RESPONSE

The average unadjusted poor immunological response rate for all the clinics was much lower after 12 months of treatment than after 6 months of treatment. Similarly, for each of the 15 clinics, the unadjusted poor immunological response rate dropped marginally for nearly all the clinics after 12 months of treatment compared with the outcome after 6 months of treatment.

5.2.1 Clinics' poor immunological rates by the case-mix adjusters

The patient-level risk factors that were found to be strongly associated with poor immunological outcome at both treatment periods were male gender, older age, AZT based regimen, and Christianity. The distribution of these confounding factors was found to be similar after both 6 and 12 months of patient treatment. For each clinic, the percentage of females was found to be more than that of males and even more than double for the combined data set. The estimated poor

immunological response rate for females in all the clinics was lower than that of males. These results are consistent with those from other studies[14,64] that showed better outcomes for women than for men. However, in only two clinics was there an indication of some difference in the outcome between males and females. Similarly, differences in poor immunological response rates by type of treatment regimen (especially between AZT based regimen and d4T based regimens) were indicated in more than half of the clinics.

Two case-mix adjusters, that is, age group and religion did not produce statistically significant differences in the estimated rate of poor immunological outcome in any of the clinics. Nevertheless, in all the clinics, the outcome for Christian patients was higher (worse) than that of patients in 'Other' religions, as was the outcome of relatively older patients.

5.2.2 Comparison by the two logistic regression (LR and LRD) models

These two models differ in that LRD model incorporates indicator variables to represent effect for clinics unlike the LR model which doesn't.

5.2.2.1 After 6 months of treatment

The likelihood ratio test statistics between each of the two case-mix adjusted variants of logistic regression (LR and LRD) model and their null counterparts were chi2(8)=129.07, pr=0.0000 and chi2(8)=104.76, pr=0.0000 for LR and LRD models respectively. This shows that case-mix explained some of the variation in the observed poor immunological rates between the clinics. The correlation coefficients of the ordered ART provider ranking of poor immunological outcome by clinics from the two case-mix adjusted logistic regression models (LR and LR-D) with their null counterpart models are 0.83 and 0.91 respectively. This shows that the rankings of some providers changed their magnitude relative to other clinics after case-mix adjustments. Notable changes involved CUL whose SIR went down compared with that of PAH, LAU and ODI. CUL had a high percentage of patients that were males, in age group 46-72 years, on AZT based regimen and Christians compared with PAH, LAU and ODI (Table 2). All these

factors were associated with poor immunological response. Similarly, LRH had high percentage of patients that were males and on AZT based regimen compared with DGM, KTM and STB (Table 2). After case-mix adjustment, the SIR of LRH went down relative to that of DGM, KTM, and STB.

The ordered SIRs by clinics from the LR and LRD models are comparable as indicated by the correlation coefficient of 1.00 and 0.97 for the case-mix unadjusted and adjusted models respectively. After case-mix adjustment, no clinic had a SIR that was significantly different from each other, but KTM and DKC showed that they had observed cases of poor immunological outcome that were significantly above the overall (cases for all clinics) observed cases of poor immunological responders.

5.2.2.2 After 12 months of treatment

The likelihood ratio test statistics between each of the two case-mix adjusted variants (LR and LRD) of logistic regression model and their null counterparts were chi2(8)=53.26, pr=0.0000 and chi2(8)=48.10, pr=0.0000 for LR and LRD models respectively. These values have drastically dropped to less than half their respective values after 6 months of treatment. This shows that the effect of case-mix adjustment after 12 months of treatment, though significant is not as strong as it was after 6 months of patient treatment.

Minimal effect of case-mix adjustment after 12 months of treatment is also shown in the way the ART provider ranking are ordered before and after adjustment, as very little changes occurred in the ordering of the SIRs (c.f. Figure 5 and Figure 7). A further indicator of the minimal effect of case-mix on poor immunological rate variation between the clinics after 12 months of treatment compared with that of after 6 months of treatment is the difference in the values of the likelihood ratio test statistics between the LR and LRD models before and after case-mix adjustment. Before case-mix adjustment, the likelihood statistic (LR vs. LRD) value was 64.36, but dropped to 59.20 after case-mix adjustment (64.36-59.20=5.16 or 8% drop: Table 12).

5.2.3 Comparison by multilevel logistic regression (MLLR) model

5.2.3.1 After 6 months of treatment

The variance of the clinics' random effects dropped by a big margin (0.077-0.020 = 0.057 or 74% drop) between the two multilevel (unadjusted and the adjusted with patient-level covariates) models. This implies that much of the statistically significant differences observed in the crude random effects between the clinics were due to differences in the patient composition between the clinics. This is further given credence by the likelihood-ratio test statistic between the two models (chi2(14) = 111.75, pr=0.0000) which shows that case-mix explains some of the variation in poor immunological rates between the clinics. The correlation coefficient of the ordered clinics' random effects by the two variants of multilevel models was 0.93, which indicates some change in their values for some clinics after case-mix adjustment. Notable changes involved CUL whose random effect decreased, and KTM and PWH both whose random effects increased relative to other clinics.

After case-mix adjustment, neither clinic had random effects that were significantly different from each other nor was there any clinic that had random effects significantly lower or higher than the overall mean (zero). This latter result is quite different from what was shown by the case mix adjusted LR models, where two clinics had poor immunological rates that were above the mean rate.

5.2.3.2 After 12 months of treatment

The variance of the clinics' random effects, unlike in the case after 6 months of treatment, dropped by a small margin (0.543-0.528 = 0.015 or 2.8% drop). This shows that much of the variation in the clinics' poor immunological rates is due to differences between the clinics rather than due to differences in the patient composition within them. The likelihood-ratio test statistic (chi2(14) = 47.95, pr=0.0000) between the unadjusted MLLR and adjusted MLLR models still shows that model with case-mix adjustment is preferred over that without adjustment, but its value drops to less than half the value obtained between the same models after 6 months of treatment.

Another indicator showing that the effect of case-mix adjustment was minimal is in the order of clinics' random effects by the MLLR model before and after case-mix adjustment as very little changes seem to have taken place in the way clinics' random effects are ordered (c.f. Figure 6 and Figure 8). The correlation coefficient between the order of the random effects by the two kinds (unadjusted and adjusted) of MLLR model was 0.95.

5.2.4 Comparison by the two types (LR & LRD vs. MLLR) of models

The confidence bands for the ordered SIRs by ordinary logistic regression are quite wide for those clinics with small sample sizes (KAL, KGH, MAM and PWH) unlike those of the random effects from the multilevel model which are more moderated and don't appear too much different compared with those of other clinics. This shows that comparison by LR is only ideal when sample sizes are sufficiently large.

In the ordinary logistic regression, estimation of standard errors is solely based on the random variation of patients within providers, without considering the random variation between providers. This has the effect of underestimating the amount of variability present, and may lead to confidence intervals that are too narrow[79]. A comparison of the LR and multilevel model display this scenario. The confidence intervals for clinics with large sample sizes are narrower for the LR model than for the multilevel model. The multilevel model on the other hand deals with this problem by incorporating clinic variability in estimating the standard errors[79].

5.3 VIROLOGICAL RESPONSE

Younger patients were more likely to have poor virological response compared with older patients. This is in line with previous studies that have shown similar trends[11,48,50]. Poor virological response rate was also found to be slightly high after 12 months of treatment compared with that of after 6 months of treatment. These results are similar to those reported in a previous study[56].

The logistic regression model with indicator for clinics, as well as the multilevel model showed that there were no clinic effects. After adjusting for confounding factors, LRH which was the only clinic that was significantly above the overall rate under the case-mix unadjusted model was marginally shown not to be significantly different any more. The comparison of clinics using the unadjusted and case-mix adjusted model show minimal changes in the order of clinics' SIR.

5.4 STUDY IMPLICATION

In healthcare provision, assessing performance whether structural, process of service delivery or clinical outcomes as a measure of quality of care can serve either internal or external purposes. An internal quality system, or benchmark, could be an initiative on the side of the hospital with the sole purpose of wanting to know how it is performing in healthcare provision as well as on patients' outcomes, with a view to quality improvement, while the external purpose would mostly serve as a way of accountability to governments, funding agencies or any other stakeholders[80]. These purposes could however be interrelated, since feedback on relatively poor performance measured externally might be an incentive to stimulate continuous quality improvements internally.

Three main reasons to support the policy of publishing clinical outcome data have been suggested; 1) to stimulate action, 2) to promote public trust, and 3) to support patient choice[81]. Although there is scanty evidence to show the effects of public disclosure of comparative outcomes data, it has been found that the publication of health outcome data stimulates quality improvement activities at the hospital level[82]. It has also be suggested that there could be several potential gains from the publishing of performance data, but use of the information by provider organizations for quality improvement may be the most productive area for further research[25].

Those against the publishing of outcome data for quality improvement suggest that those who wish to improve care for patients should concentrate on direct measurement of adherence to clinical and managerial standards and only use outcome data for research and monitoring trends within an organisation[42]. This is

because the use of comparative outcome performance data could be misused to support a system of reward and punishment and would often be resisted by clinicians and managers.

In health provider profiling, it is important to be able to correctly identify those providers that are low outliers in terms of having low rates of poor response so that the reasons for their excellent performance can be elucidated and imitated by other providers. Similarly, providers that are high outliers by having high poor response rates to ART need to be correctly identified so that the reasons for their poor performance can be corrected or modified[83]. This is why it was imperative to account for confounding factors. After the adjustment for difference in case mix, clinics treating more risky patients are reassured that they will not be unfairly compared. Furthermore, because of the expense associated with conducting internal performance audits, one would want to target such interventions only at providers that had unacceptably high rates of clinical response.

Considering the analysis of immunological response, where the logistic regression model moderately described the data, the study has demonstrated the following:

First, the importance of case-mix adjustment was demonstrated:

i. After, 6 months of treatment, the odds ratio in the case-mix adjusted logistic regression (LRD) model for nearly all of the clinics changed substantially compared with those of the unadjusted logistic model. Before the adjustment 8 clinics had odds that were significantly different from that of the clinic (JUB) with the lowest crude response rate. After adjustment only 4 clinics had odds that were significantly different from that of JUB. Similarly, the number of clinics that had outlying standardised incidence rates (SIR) of poor immunological outcome in the unadjusted model reduced after adjusting the model for case-mix.
ii. The likelihood test statistics between the unadjusted and the adjusted logistic regression (LR & LRD) models showed that case-mix explained much of the variability in the outcome (poor immunological response)

iii. There was a significant decrease in the variance of the random effects for the clinics between the multilevel models without and with case-mix adjustment, the difference being what is explained by the case-mix.

iv. A number of clinics changed their SIR or random effects and subsequently ranks after accounting for confounding factors. Of particular note are CUL and LRH which changed ranks by 4 positions (down and up respectively) after adjusting for the unfavourable/favourable risk factors.

Secondly, the study also has shown that for those clinics with small sample sizes, the estimates from the fixed effects models (LR and LRD) are very imprecise (wide confidence intervals) unlike those from the multilevel logistic regression (MLLR) model. This is because multilevel models do account for variation by chance by allowing imprecisely estimated outcomes from small clinics to 'borrow' information from other clinics, causing their estimates to shrink towards the overall mean. The study has shown from the case-mix adjusted multilevel analysis that no clinic was significantly different from each other or significantly above or below the overall mean. In the fixed-effect modelling (LR&LRD), variation by chance had a large impact on the conclusions drawn about the clinics.

The WHO patient monitoring guidelines for HIV care and antiretroviral therapy (ART) have indicated that increase in CD4 count by a certain acceptable margin compared with baseline value may be a measure of ART success. On the same line, data on groups of patients may be collected and summarised at the facility (clinic) level as performance measures (for quality improvement) for clinical teams[5].

The motivation for this study was that the findings may be useful in improving quality of care in the management of HIV positive patients on ARV, rather than just flagging clinics as underperforming or over performing. The focus of the study was on outcome (immunological and virological response) rather than on the process of service delivery. The results may be used both internally (clinic) or

externally (e.g. Tshwane District Health department, or supporters such as the FPD). Clearly after 6 months of patient treatment, there were no statistical differences in poor immunological rates between the clinics, but absolute SIR values for PAH and LAU were below the average, while those of DKC and DGM were above the average. Clear differences in the clinics' SIR of poor immunological response emerged distinctively after 12 months of treatment, but PAH and LAU were the only two clinics that had SIRs below the average, while DGM and DKC were again among the clinics that had SIRs of poor immunological outcome above the mean. Probably there are better patient management practices or resources in PAH and LAU that could be learned and adopted by the other clinics. Similarly, there could be negative factors associated with the four clinics' with the highest poor immunological response rates that may be identified and modified. The decision lies with the ART managers and programmers.

5.5 CONCLUSIONS AND RECOMMENDATIONS

The objectives of this study were to 1) identify factors that are associated with immunological and virological responses for adult HIV patients on ARV, and 2) compare clinics' performances on these two indicators using risk adjusted logistic regression and multilevel models. The study showed major risk factors for poor immunological response as male gender, AZT based drug combination, Christian religion and older age, while the major risk factors for poor virological response were identified as low CD4 count and younger age. The study has also shown that under the logistic regression modelling, the odds ratios or the ratio of observed to expected cases of poor immunological and virological outcomes for clinics changed after case-mix adjustment. In the multilevel modelling, there were also noticeable differences in the values of the clinic specific effects between the unadjusted and adjusted case-mix models.

The logistic regression models in this study showed estimates with wide confidence intervals for clinics with small sample sizes unlike in the multilevel analysis, where the confidence intervals were not noticeably different from those

of clinics with acceptable sample sizes. The multilevel analysis also showed that no clinic was significantly different from each other in terms of poor immunological response rate after 6 months of treatment, but differences emerged after 12 months of treatment where two clinics (LAU and PAH) exceeded expectation by having poor immunological response rates below the overall mean rate.

Based on these findings, the following conclusions and recommendations can be made:

5.5.1 Limitations of the study

i. The number of patient records without baseline CD4 count and viral load was high and this made some clinics to have inadequate sample sizes, which consequently caused some of their confidence intervals for the SIR computed from the ordinary logistic regression to have negative values.
ii. The data used for the 12 month treatment period was not all from those patients whose data was used in the 6 month period.
iii. The sample size after 12 months of treatment, though quite large was relatively smaller than that after 6 months of treatment, and this difference could be responsible for the difference in immunological outcome observed between the two treatment periods.

5.5.2 Recommendations from the study

i. The importance of case-mix adjustment was clearly shown from the results of this study. It is therefore recommended that confounding patient and other factors that may affect the outcome be properly accounted for whenever grouped patients outcomes are to be compared across healthcare providers in order to make credible comparison of the outcomes.
ii. The study also showed that the number of clinics being flagged as outlier by the ordinary logistic regression (LR&LRD) models were in some instances more compared to the number flagged by multilevel logistic regression (MLLR) model. This is because the ordinary logistic regression

model may have underestimated the standard errors of the estimates. It is therefore recommended that multilevel logistic regression be used whenever its basic assumptions for analysis are met (e.g. data is hierarchical and group size, e.g. healthcare providers is 20 or more).

iii. Since it is important to have baseline measurements to meaningfully assess treatment response, it is recommended that ART data managers enter into the electronic system, the CD4 count and viral load measurements taken at the time of the HIV screening.

5.5.3 Conclusions

i. It can be concluded that after 6 months of patient treatment, case-mix explained much of the differences in the clinics' poor immunological outcome, while after 12 months of treatment clinic specific unmeasured/unobserved effects explained much of the differences in poor immunological response between them. In the initial stages of ARV treatment, patients' baseline characteristics play a major role in determining immunological outcome, but as time goes on, the clinics play a major role in determining the outcome.

ii. In making comparison of ART outcome indicators, it is necessary to account for confounding factors before comparing programs, providers or cohorts

iii. All the clinics managed to keep poor virological response rate controlled between the two treatment observation times.

iv. The programmers and managers of ART program within the clinics under study are to be commended for striving to ensure standard and controlled rates of poor virological outcomes betweens the clinics.

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